



GRAVES' DISEASE & THYROID FOUNDATION

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Treatment of Graves' Disease – An Overview by Robert Volpé, M.D.

Hyperthyroidism may be defined as the excess production of thyroid hormones. The most common cause is Graves' disease. Less common causes include toxic adenoma of the thyroid, the hyperthyroid phase of thyroiditis, and hyperthyroidism due to hydatidiform moles or choriocarcinoma. Rare causes are pituitary thyroid-stimulating hormone (TSH) excess, widespread functioning metastatic thyroid carcinoma, and excessive ingestion of thyroid hormone. We shall concern ourselves here primarily with the treatment directed to counteract the thyroidal overactivity.

Graves' Disease

This disease is considered to be an autoimmune disorder. The most likely possibility is that it results from a defect in immune regulation causing activation and expansion of clones of thyroid-directed lymphocytes (which normally would be suppressed) to survive, interact with an

antigen on the thyroid cell membrane, and then produce an antibody (thyroid stimulating immunoglobulin) against the TSH receptor (1,2). This antibody has the peculiar (if not unique) capacity to be able to attach to the TSH receptor (presumably by an antigen-antibody union), and then to stimulate the thyroid cells in a manner similar to that of TSH (3).

Since Graves' disease thus appears to be an autoimmune condition, rational therapy would be to interfere with the specific autoimmune process. This, however, is not yet practicable, and thus therapy continues to be aimed at the control of excessive thyroid hormone production, either by suppression (antithyroid drugs) or destruction of tissue (radioactive iodine or subtotal thyroidectomy). Non-specific forms of therapy that are also useful include rest, sedation, and sympathetic blockers. Of these last agents, propranolol has been shown to relieve symptoms, and even though it does not interfere with thyroid

function, it may bring about remissions in Graves' disease.

Thyroidectomy

[Editor's update: new guidance was released in 2011 stating that near-total or total thyroidectomy is now the procedure of choice for patients undergoing this treatment option. For more info, please see "*Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists*" by Bahn, et. al at thyroidguidelines.net.]

Historically, thyroidectomy was the first effective therapy for hyperthyroidism (4). However, it did not really become feasible until Plummer (5) in 1923 demonstrated the value of iodine in the preparation of patients for surgery. Iodide was shown to reduce vascularity of the gland and to produce a temporary involution. It did this by interfering acutely with the release of thyroid hormone and

with the biosynthesis of thyroxine (6), the latter effect was prolonged, and in some patients persisted almost indefinitely when the iodide therapy was continued. This form of preoperative preparation with iodide made it possible to operate on patients who were no longer severely hyperthyroid, and this reduced the incidence of complications considerably. Later, the introduction of antithyroid drugs (7) made it possible to have even more effective preoperative preparation. At the present time, with advances in anesthetic techniques, surgical procedures, and postoperative care, the mortality of thyroidectomy is virtually nil.

Many centers in the world continue to prefer subtotal thyroidectomy (4,8) as the optimal form of definitive therapy for Graves' disease, although in Toronto most endocrinologists regard thyroidectomy as the treatment of choice only in selected patients, particularly children or adolescents who cannot be controlled with antithyroid drug therapy (9). It is, of course, accepted that the patient must be rendered euthyroid before surgery by the administration of antithyroid drug therapy for some weeks, often with the addition of iodine in the last few days. Associated disorders

must be treated accordingly; e.g., a patient with cardiac disease should be digitalized and arrhythmias must be corrected or controlled before surgery. Diabetes mellitus, if present, should also be properly controlled.

Although it is generally a safe procedure, subtotal thyroidectomy is still attended by a variety of complications. It is noted that from 3.6 to 42.8% of patients develop hypothyroidism postoperatively, either shortly after the procedure or many years later. The higher incidence was detected by follow-up studies many years after surgery, so that it would appear that the thyroid remnant is incapable of continued secretion beyond a limited period in many patients (9).

The onset of hypothyroidism may be subtle and often may go undetected for many years while the patient's health gradually deteriorates. The cause of this late postoperative deterioration may be due, at least on some occasions, to autoimmune destruction.

Consequently, it is clear that annual follow-up is essential, even in those patients who do exceedingly well. Patients who have transient hypothyroidism after an

operation are particularly prone to develop permanent myxedema later. The presence of thyroid autoantibodies in moderate or high titers at the time of surgery may also be a harbinger of hypothyroidism.

Postoperative hypoparathyroidism will develop in about 1% of patients following subtotal thyroidectomy, and indeed in occult form may occur in up to 10%. Patients with the overt form of this condition must be treated with lifelong calcium and vitamin D therapy. Untreated hypoparathyroidism is associated with a high incidence of cataracts, convulsions, and metastatic calcification. Vocal cord palsy due to trauma of the recurrent laryngeal nerve is usually unilateral and occurs in 0 to 5.6%. At the very least, this complication alters the voice, particularly for singing, and usually results in chronic hoarseness. Paralysis of both cords produces spastic airway obstruction and may require tracheotomy.

The persistence of hyperthyroidism has been observed in 0.6 to 17.9% of patients, and is more common in children. A variety of other complications has been described, such as bleeding, scars, keloid formation, wound infections, and phlebitis. It should be emphasized,

however, that in general subtotal thyroidectomy is an extremely effective form of therapy which controls the disease in 90% of patients quickly and well.

Radioactive Iodine

Since the thyroid gland is the only tissue to retain iodine for any prolonged interval, it is an ideal organ for the use of therapeutic radioactive iodine (10). I-131, with a half-life of eight days, has been the isotope of choice since 1946. This isotope is largely a beta-emitter, only about 10% of its effect is derived from gamma-emission. Because the beta-rays travel only about 2 millimeters, the I-131 within the thyroid gland will not damage surrounding structures, and therefore considerable radiation can be applied to the gland. The radiation destroys some cells, leaves others intact, and in some, effectively reduces the synthesis of hormone. In many centers it has become the treatment of choice for adult hyperthyroidism. It has many advantages: the treatment is usually definitive; it is convenient; and it can generally be administered without admitting the patient to the hospital. It avoids the morbidity and complications of surgical treatment. Only rarely is I-131 administration followed by radiation

thyroiditis with tenderness in the neck and an increase in hyperthyroid symptoms.

The first clinical effects of radioactive iodine become evident no earlier than one month, with gradual improvement following treatment in most patients. The goiter usually disappears or diminishes in size. About 80% of patients become euthyroid after one dose, while most of the remainder require only a second dose. Only a small percentage require three or more treatments. There is no accurate means to determine the precise dosage, and the physician often applies a "guesstimate," based on the estimated weight of the thyroid gland by palpation and the radioactive iodine uptake. In Toronto, we prescribe 100 microcuries per estimated gram of thyroid tissue when the 24 hour radioactive iodine uptake is approximately 50%. If the radioactive iodine uptake is considerably higher than this, the dosage is reduced somewhat. If the uptake is lower than 50%, the dosage is increased slightly. Generally physicians tend to overtreat small goiters and increase the incidence of hypothyroidism. Large goiters are often undertreated. It has been shown that using much more sophisticated techniques does

not provide better results. Furthermore, there does not appear to be any great advantage in reducing the dosage, since this merely increases the number of patients who are still hyperthyroid three months after the initial dose, and does not prevent the late onset of hypothyroidism once the hyperthyroidism has been controlled (although it may delay that onset for several years).

Hypothyroidism is the only significant adverse effect of radioactive iodine therapy. In our hands, about 20% of patients become hypothyroid within one year; thereafter, the incidence gradually increases so that about 50% are hypothyroid within a decade (11,12). Follow-up must be continued, not only in the early months following radioiodine therapy, but on an annual basis forever. Since the onset of hypothyroidism may be subtle, the patients must be exhorted to return for annual examinations to check their thyroid status. However, once patients have become hypothyroid and are taking thyroxine therapy, the chief point of follow-up is to ensure that they continue to take their medication.

Radioactive iodine seems to prevent replication of thyroid cells, and thus late hypothyroidism may be a consequence of the body's

failure to replace cells that wear out. This failure may also be due to autoimmune destruction stimulated by irradiation applied to an already susceptible gland.

The other possible hazards of radioactive iodine are largely hypothetical. Abnormalities of leukocyte chromosomes have been reported after I-131 therapy, but the increased incidence of leukemia predicted following the use of radioactive iodine in hyperthyroidism has not materialized. There is, however, a slightly increased incidence of leukemia in Graves' disease generally, no matter what form of treatment is prescribed, and it seems to be unrelated to that treatment¹³.

There has been no increased incidence of mutations secondary to gonadal radiation by radioactive iodine. The radiation to each ovary is approximately 0.12 rad/millicurie¹⁴. The conventional dose of radioactive iodine delivers approximately the same dose of radiation to the ovaries as does roentgenological examination of the colon or kidneys. The dose of radioactive iodine usually employed in hyperthyroidism would thus produce only a small amount of gonadal radiation, and as a "genetically

significant gonadal dose," this source does not contribute nearly as much to the whole of the North American population as does diagnostic radiology (10).

Concern has been expressed that radioactive iodine might produce carcinoma of the thyroid because it is well known that radiation to the neck in childhood or adolescence is one of the major causes of thyroid carcinoma. However, the doses of radiation which induce thyroid carcinoma must be low; in the order of 50 to 1, 500 rad. As the doses of radiation become higher, the incidence of carcinoma of the thyroid declines sharply (15). It would appear, therefore, that our concern can readily be allayed, because the dosages used for the treatment of hyperthyroidism are much greater than those referred to previously, and are often in the order of 7, 000 to 10,000 rad. Indeed, the incidence of thyroid carcinoma in patients who have received radioactive iodine therapy for hyperthyroidism appears to be lower than that in the general population¹⁶. The low incidence of thyroid carcinoma after it may be due to the same reason that so many patients become hypothyroid following such therapy: the radiation in the

doses used impairs the ability of the cells to replicate (13).

[Editor's update: new guidance was released in 2011 regarding the use of radioiodine treatment in patients with mild and moderate-to-severe ophthalmopathy. For more info, please see "*Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists*" by Bahn, et. al at thyroidguidelines.net.]

Drug Therapy

[Editor's update: new guidance was released in 2011 regarding reduced initial and maintenance dosing of Tapazole® and PTU. The guidance also states that PTU is associated with an unacceptable risk of liver failure in children and that methimazole (brand name Tapazole®) is preferred over PTU for all patients, except in select circumstances. For more information, please see "*Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists*" by Bahn, et. al at thyroidguidelines.net.]

The two main groups of specific antithyroid drugs currently used in the therapy of hyperthyroidism are the thiourea group, for example propylthiouracil (PTU), and the imidazole group, of which methimazole only is available in North America (9,17). In ameliorating hyperthyroidism, PTU has three known actions (17): it inhibits the peroxidase enzyme system, thus preventing oxidation of trapped iodide and subsequent incorporation in iodotyrosines and ultimately iodothyronine; it inhibits coupling of the iodotyrosines; and finally it inhibits the conversion of L-thyroxine to L-triiodothyronine (T3) in peripheral tissues. The imidazole group appears to act only on the peroxidase enzyme system. There is, however, little to distinguish the two groups in terms of clinical response. PTU is often prescribed in doses of 100 to 200 milligrams every eight hours – or methimazole, 10 to 20 milligrams every eight hours. The duration of action of these drugs is approximately eight hours. Nevertheless, once patients are under control, PTU in single doses of 50 to 100 milligrams per day will often maintain the patient in a euthyroid state. Nevertheless, daily dosages may vary considerably depending on the response, and some control. The timing of clinical improvement will depend on

the amount of thyroid hormone stored within the thyroid gland, because the drugs do not interfere with the secretion of preformed hormone. Improvement usually is evident within three weeks, and a euthyroid state may be achieved within six to eight weeks. The dosage is then gradually reduced, although it is necessary to continually titrate the dosage against the patient's response. Estimations of serum thyroxine are very useful for this purpose.

If the goiter enlarges during therapy, this may be due either to progression of the basic underlying disease or to the development of PTU-induced hypothyroidism. If the serum thyroxine declines below normal and plasma thyrotrophin rises, it is important to reduce the dosage of PTU rather than adding thyroxine.

Complications of Drug Treatment

The most serious side effect is agranulocytosis, which is observed in 0.4 to 0.7% of patients. This complication develops precipitously and there is thus no point in performing routine or frequent leukocyte counts. However, the harbingers of agranulocytosis include severe pharyngitis with or

without fever and rashes. If the patient develops any of these symptoms the medication must be discontinued and an immediate leukocyte count performed. Thus, patients should be warned about these symptoms and advised to discontinue the medication and report to the physician immediately. Fortunately, the agranulocytosis is usually reversible. More common but less severe side effects include dermatitis, arthralgia, myalgia, jaundice, hepatitis, fever, and lymphadenopathy. Very rarely has aplastic anemia been reported (9,18). Although the physician could resort to another type of antithyroid drug when a serious complication develops, most endocrinologists prefer to use destructive therapy rather than continue an antithyroid medication.

Long-Term Remissions

The objective of therapy is to attain control of the disorder (maintenance of a euthyroid state) and ultimately to bring about a long-term remission (characterized by the maintenance of a euthyroid state for at least some months after cessation of antithyroid drug therapy). When therapy is continued for six to twelve months, remission rates of up to 50% have been reported; my own experience suggests long-term remissions in the order of 30 to 40%.

About half the patients who remain in remission after cessation of the medication will suffer a recurrence sooner or later. A second exacerbation should be treated with destructive therapy rather than submitting the patient to repeated intervals of remission and exacerbation. Reduction in the size of the goiter during the course of the antithyroid drug treatment suggests that remission is occurring. Studies of thyroid suppressibility have not proved to be precise parameters of remission. However, the use of the thyroid-stimulating immunoglobulin (TSI) assay as a predictor of remission may prove useful since most remissions are accompanied by a disappearance of TSI (19).

It is my view that all patients with Graves' disease who have moderate-sized or small goiters (less than 45 grams) should be treated with an antithyroid drug for at least six months. Only when this is inconvenient should early destructive therapy be used. In my experience, remissions rarely occur with larger goiters, and in these ablative therapy may be used as initial treatment. Other indications for antithyroid drugs include long-term therapy in childhood and adolescence, as preoperative therapy, and therapy for hyperthyroidism during

pregnancy (to be discussed separately). In addition, antithyroid drugs should be administered before radioactive iodine therapy in elderly patients and in those with severe associated diseases in whom transient post I-131 thyroiditis might produce a temporary but dangerous increase in plasma thyroid hormone levels. Such patients should be rendered euthyroid before I-131 therapy. It should, of course, be emphasized that the antithyroid drug must be discontinued at least 48 hours before radioactive iodine is administered.

Those patients who do not undergo remission after a course of antithyroid drug therapy require ablative therapy either with surgery or with radioactive iodine. In Toronto, radioactive iodine is the definitive treatment of choice in adults with hyperthyroidism (10).

There is no evidence that antithyroid drugs per se alter the course of the disease, even though they suppress the production of thyroid hormone and bring about a euthyroid state. Why remissions can be induced in 30 to 40% of patients with Graves' disease is not fully understood at the present time, although the reader is referred elsewhere for

speculations about such remissions (1,2); in any event, most remissions appear to be immunological, since all stigmata of the immunological abnormalities disappear with drug-induced remissions (19). As mentioned previously, therefore, estimations of TSI may prove to be the most useful means for determining whether remissions have actually occurred. It should also be emphasized that remissions may also occur as a result of progressive autoimmune destruction, and that years after antithyroid drug therapy, some patients with Graves' disease will even develop spontaneous hypothyroidism (20).

Other Drugs

Iodide is not an ideal agent for the long-term treatment of hyperthyroidism because its therapeutic response is frequently incomplete or transient. It is used in the last few days of preoperative preparation along with an antithyroid drug (9), or in the treatment of thyroid storm, again in combination with an antithyroid drug.

Lithium carbonate has effects similar to those of iodide. However, the place of lithium in the treatment of hyperthyroidism remains to be defined, and this agent should be considered experimental (21). Drugs that deplete

catecholamines may also be useful as adjuncts in the treatment of hyperthyroidism. Both reserpine and guanethidine suppress the clinical symptoms of hyperthyroidism caused by the increased action of sympathetic amines, although they do not appear to affect tissue hypermetabolism. Propranolol, a potent beta-adrenergic blocking agent, has a prominent position in the treatment of hyperthyroidism (22). It has no effect on the fundamental disease, but it can ameliorate many of the signs and symptoms. Rapid heart beat is controlled, nervousness declines, and sweating and tremor are reduced. The patient generally feels much improved. Improvement has also been noted in myocardial efficiency, and the exaggerated myocardial oxygen consumption has been reduced. Propranolol has been useful as symptomatic therapy while awaiting the improvement from antithyroid drugs or radioactive iodine. Some patients have even gone into remission on propranolol therapy alone. These drugs should be used cautiously when there is evidence of myocardial insufficiency, although control of tachycardia in Graves' disease often permits improved circulatory efficiency. Propranolol is usually given orally in doses of 20 to 40 milligrams every six

hours. In thyroid storm it may be given in 1 to 3 milligrams over 3 to 10 minutes.

Special Considerations

Treatment of Children – Hyperthyroidism is comparatively rare in young children (9). Generally antithyroid drug therapy is preferred in children and adolescents, and treatment for two years or longer is recommended.

[Editor's update: new guidance was released in 2011 stating that PTU is associated with an unacceptable risk of liver failure in children and that methimazole (brand name Tapazole®) is the preferred antithyroid drug, except in select circumstances. For more information, please see "*Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists*" by Bahn, et. al at thyroidguidelines.net.]

If remissions do not occur, and if the disorder cannot be controlled with antithyroid drugs, most conservative clinicians recommend subtotal thyroidectomy, at least until about age 20, even though the complications of

thyroidectomy appear to be more frequent in children (perhaps because the structures are smaller). Radioactive iodine has been advocated by some groups for use in children and adolescents (23), although it has not received wide approval. While the fear of carcinogenesis seems unfounded, a longer period of follow-up is still required before radioactive iodine is approved for wider application in children.

Pregnancy – Radioactive iodine is contraindicated in pregnancy because the fetal thyroid concentrates iodine after the twelfth week of gestation. However, radioactive iodine therapy has been prescribed inadvertently to some gravid women in the first and second trimester without apparent injury to the fetus. Nevertheless, such risks should not be taken knowingly, and it is wise to ensure that women are not pregnant before radioactive iodine is administered. Surgery is to be avoided in the first trimester because it results in a high incidence of spontaneous abortion, although it seems reasonably safe in the second trimester. Generally the hyperthyroid state during pregnancy is treated with antithyroid drug therapy (9,18). It is our practice to continue antithyroid drugs throughout the period of gestation. In the early part of pregnancy, the usual dosages of antithyroid drugs are

used, as has been discussed previously. However, the drugs cross the placenta, and if the dosage is excessive may produce goiter and hypothyroidism in the fetus. Such goiters may be of a size that will interfere with vaginal delivery. Thus, particularly in the latter part of the second trimester and throughout the third trimester, dosages must be reduced considerably; doses of PTU below 200 milligrams per day have not been reported to produce goiter in the newborn. The dose of PTU during pregnancy must be titrated to ensure that the mother does not become hypothyroid because this state is associated with an increased incidence in spontaneous abortion. Aside from maternal hypothyroidism, there is no point in adding thyroxine to the mother's treatment during this stage of pregnancy because thyroxine does not traverse the placenta. In the latter part of gestation, it is therefore important to reduce the dose of antithyroid drug to low levels, even if this results in a slight return of hyperthyroidism. Following delivery, the mother should not nurse because the antithyroid drug (which should be continued following delivery) is secreted in the mother's milk. On the other hand, it may be possible to discontinue therapy at that time if there is

evidence that the mother is in a state of remission.

Thyroid Crisis – Thyroid crisis (thyroid storm) is a lifethreatening condition that is characterized by the greatly heightened signs and symptoms of hyperthyroidism and by hyperpyrexia. The elevation in body temperature may reach 106 degrees F and be associated with marked restlessness, agitation, severe tachycardia, heart failure, profound prostration, nausea, vomiting, diarrhea, delirium, psychosis, jaundice, and subsequent dehydration. The disorder is now rare. Factors that precipitate this crisis include infections, trauma, surgery, and withdrawal from antithyroid drugs. Treatment is usually commenced with iodide because this drug reduces the secretion of thyroid hormone very quickly. Doses of 500 milligrams every six hours orally, or 0.5 grams of sodium iodide in a constant intravenous drip every eight hours should be used. It is important to give propylthiouracil in doses of 300 to 600 milligrams per day before giving the iodine so that synthesis of thyroxine will also be quickly blocked if iodine is prescribed first there may be a considerable delay in the response to the antithyroid agent. Propranolol, intravenous fluid

therapy, the mechanical treatment of hyperthermia, and corticosteroid may also be used during this emergency.

Summary

Hyperthyroidism is of several types, although Graves' disease is by far the most common. For young people, pregnant women, and patients with recent onset of hyperthyroidism, antithyroid drugs should be the first approach to treatment. About 30% of patients with Graves' disease will go into a long-term remission following a course of such drugs. If antithyroid drugs are attended by complications, difficulties in control, or subsequent recurrences, patients then require definitive therapy. In our view, radioactive iodine is indicated for the treatment of hyperthyroidism in patients with large goiters, with complicating medical illnesses, for hyperthyroidism recurring after antithyroid drugs, and in elderly persons. Radioactive iodine has the advantage that it is simple and painless. Its only disadvantage is the high incidence of post-I-131 hypothyroidism, which appears early or late after this therapy. An increase in carcinoma of the thyroid following the use of radioactive iodine has not been demonstrated, and is unlikely to appear, nevertheless, another decade should pass before children or adolescents are treated with this agent. Subtotal

thyroidectomy is still an effective form of treatment for hyperthyroidism, and is the treatment of choice in many centers. However, complications such as hypoparathyroidism and recurrent laryngeal nerve palsy occur with sufficient frequency to make this therapy less attractive to us than radioactive iodine.

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