Physiologic, Pharmacologic and Therapeutic
Considerations in Surgery
for Hyperthyroidism

Herbert A. Selenkow, M.D., and Charles S. Hollander, M.D.

The evolution of the surgical treatment of hyperthyroidism marks an historic epoch in medicine. Today, the predictable accomplishment of thyroidectomy for this disorder stands in sharp contrast to the prohibitive risks and devastating results which prevailed prior to antithyroid therapy. The development of inhalation anesthesia was followed by remarkable advances in operative technique by such notable surgeons as Bilroth, Kocher and Halsted. However, despite great technical skill, operative correction of hyperthyroidism was hampered for years by lack of an effective euthyroid to tolerate the rigors of general anesthesia and thyroidectomy. Introduction of the use of iodides by Plummer afforded some measure at least of preoperative amelioration, and significantly reduced surgical morbidity and mortality. The discovery of antithyroid compounds and their application to the treatment of hyperthyroidism has permitted the performance of thyroidectomy as an elective procedure. The anesthesiologist and surgeon may now lavish their time upon such vital problems as the conduct of anesthesia, the meticulous anatomic dissection of cervical structures and the control of hemostasis. No longer is thyroidectomy a hectic, sanguineous surgical marathon.

Successful application of clinical and pharmacologic knowledge in the preoperative preparation of hyperthyroid patients must be predicated upon a thorough understanding of the basic physiologic and biochemical alterations in thyroid function. Several reports have dealt adequately with current thinking in regard to selection of optimal therapy from the modalities available: antithyroid drugs, radioactive iodine and thyroidectomy. This report will review some of the fundamental considerations in the management of patients undergoing elective thyroidectomy for hyperthyroidism. The concepts inherent in such management may also serve as a model for the operative treatment of all goiters.

Hyperthyroidism is a complex disorder whose precise etiology is unknown. Neurohumoral factors, as yet poorly understood, interfere with the physiologic regulatory mechanisms governing the pituitary-thyroid relationship, with a consequent excessive secretion of the thyroid hormones, thyroxine and triiodothyronine. These hormones dramatically alter such physiologic functions as cardiohemodynamics, neuromuscular activity, autonomic responsiveness, temperature regulation and respiration. Such alterations reflect the ubiquitous changes at a biochemical level involving the metabolism of proteins, fats, carbohydrates, nucleic acids, vitamins, hormones, and alterations in enzyme systems. These effects of the thyroid hormones have been thoroughly characterized by the physician, the physiologist and the biochemist. Their clinical significance must be fully appreciated in order to manage patients with hyperthyroidism intelligently.

Physiologic and Biochemical Actions of Thyroid Hormones

The striking clinical features of hyperthyroidism result from acceleration of the rate of reaction of all metabolically active tissues. There is scarcely a vital physiologic process that remains unaltered. It is incumbent upon the physician, the surgeon and the anesthesiol-
ogist to insure the return to normal of these hyperactive processes for a safe conduct through thyroidectomy. The remarkable increase in metabolic activity in hyperthyroidism creates an enormous demand for oxygen which must be satisfied by the heart and circulation. Of particular importance in this regard are the marked changes in cardio-hemodynamics including an increase in blood volume, in erythrocyte mass and velocity of flow. There is a notable rise in cardiac output, in coronary blood flow and myocardial work. Interestingly, the enhanced tissue extraction of oxygen is for the most part accomplished by accelerated rate and volume of blood flow in most organs, rather than by an increased arterio-venous oxygen extraction. Renal blood flow is increased, but the cerebral and splanchnic circulations do not appear to require this adjustment. Ventilation is increased, as must be pulmonary blood flow and volume. The remarkable heat production generated by the increased oxygen utilization is dissipated, for the most part, through a tremendously dilated peripheral capillary bed. Radiation and convection, as well as the cooling effect of increased perspiration tend to maintain thermal stability. However, most patients with hyperthyroidism feel subjective warmth and, indeed, often have an increased internal body temperature.

Propulsion of the expanded volume of blood in hyperthyroidism requires augmentation of cardiac work. In patients over the age of 40 this hyperkinetic state may result in congestive heart failure and auricular fibrillation. The major portion of the increased cardiac output results from acceleration of heart rate rather than enhanced stroke volume. Tachycardia in hyperthyroidism reflects the exaggerated sensitivity of the circulation to sympathetic stimulation. This phenomenon was first shown by Goetsch in 1918, and has been amply confirmed since that time. Indeed, many of the clinical manifestations of hyperthyroidism resemble those of sympathetic stimulation and may be partially ameliorated by sympatholytic or sympathicopivic drugs such as reserpine or guanethidine.

Not only is there excessive work of the heart, but of the entire somatic musculature as well. Whether this results from the inefficient or ineffective utilization of oxidative energy or from ungoverned activity is not clear. But regardless of mechanism, there is often a remarkable loss of nitrogen, phosphorous, potassium and creatine. The muscular weakness of hyperthyroidism may at times be severe enough to mimic a primary myopathy or myasthenia gravis. Failure to allow time for correction of the cardiopathy, myopathy and profound depletion consequent to hyperthyroidism prolongs and complicates the convalescence from thyroidectomy. The skeleton also shares in the wasting. Hypercalciuria is a common finding in hyperthyroidism, but the profound skeletal changes described prior to the advent of effective therapy are fortunately now rare. Serum calcium and phosphorous levels are usually normal, although elevations occasionally have been reported to result exclusively from hyperthyroidism.

The central nervous system is influenced by the metabolic alterations in this disorder. There is evidence to suggest that emotional trauma may be an inciting etiologic factor. The hyperthyroid patient is emotionally labile, irritable, readily moved to tears and at times agitatively depressed. The ophthalmopathy so common to this illness appears to be associated with a neurohumoral abnormality, perhaps originating in the hypothalamus or pituitary gland. Evidence points to a discrete hormonal factor which has been designated exophthalmos-producing substance, or EPS.

Metabolic Pathways of Thyroid Hormones

The chemical synthesis, secretion and transport of thyroid hormones are germane to rational treatment and are worthy of brief review before consideration of the clinical aspects of hyperthyroidism.

THYROID HORMONAL SYNTHESIS

The thyroid gland normally synthesizes its two essential hormones, L-thyroxine and L-triiodothyronine, by a complex sequence of chemical reactions represented simply in figure 1. Knowledge of these reactions has clinical import. It is now possible to explain certain previously ill-defined forms of goitrous cretinism as resulting from defects in certain phases of thyroid hormonal synthesis.

These uncommon forms of goitrous hypo-
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roidism, like the more common euthyroid goiters, may share common biochemical defects. Though quantitatively different, such defects may lead to compensatory thyroidal hyperplasia via pituitary-thyrotropic stimulation. Thus, when the thyroid gland is unable to secrete sufficient hormone, hypothyroidism results. Hypothyroidism is a stimulus to release of thyrotropin which in turn causes thyroidal hyperplasia and enlargement. The hyperplastic gland may, by increase in size, compensate for the biochemical defect and produce suffi-

I. TRAPPING

- T/S gradient
- Thyroidal "trapped" I

II. BINDING

- I\(^{-}\) oxidation
- [I\(^{2-}\)] + thyroglobulin
- moniodotyrosyl (MIT)
- diiodotyrosyl (DIT) \(\rightarrow\) thyroglobulin

III. COUPLING

- 2 DIT \(\rightarrow\) thyroxinyl (T4)
- MIT + DIT \(\rightarrow\) triiodothyroninyl (T3) \(\rightarrow\) thyroglobulin

IV. RELEASING

- T4 - T3 - MIT - DIT - thyroglobulin
- enzymatic hydrolysis
- thyrotropin activated
- MIT + DIT (thyroid)

- MIT + DIT (thyroid) \(\rightarrow\) tyrosine
- deiodinase
- tyrosine + I\(^{-}\) (recycled)

Fig. 1. The intrathyroidal synthesis of thyroid hormones consists of four basic steps. Serum iodide is concentrated to initiate the process (Step I: Trapping). Note that operation of a thyroid "pump" is a prerequisite for the maintenance of a T/S gradient for iodide. Perchlorate and thiocyanate inhibit this "pump." TSH stimulates it. The trapped iodide is then bound (Step II: Binding) by the oxidation of iodide and displacement of a hydrogen from the three-position of tyrosyl residues. Thioureylenes such as methimazole or propylthiouracil inhibit this reaction. Increased levels of iodide block this process. Iodotyrosines are then coupled (Step III: Coupling) and retained in storage form as peptide-linked residues within thyroglobulin. Proteolysis releases T3 and T4 (Step IV: Releasing) for secretion into the blood. MIT and DIT also present in thyroglobulin are released but deiodinated by a potent deiodinase present in thyroid parenchymal cells. The released iodide can then be recycled for re-utilization (see text for detailed discussion).
Fig. 2. Potassium perchlorate release of trapped thyroidal radioactive iodide in a patient with hyperthyroidism. The curve of open circles represents the 131I uptake without medication. Methimazole 50 mg. was given by mouth one hour prior to obtaining the curve represented by the solid dots. One gram of potassium perchlorate was given orally four hours later. The rapid discharge of radioactive iodide indicates that the prior administration of methimazole prevented organification of the iodide which was retained in the gland as “trapped iodide.”

In an analogous manner, chemical agents may inhibit various stages of thyroid hormonal synthesis, in turn promoting thyrotropin release, thereby causing goiter. Goitrogenesis is thus a compensatory reaction of the thyroid gland that provides the necessary secretion of thyroidal hormones.

For purposes of simplification, thyroid hormonal synthesis may be divided into four phases: trapping, binding, coupling and release.

**Trapping.** Iodine enters the body via the alimentary tract either from dietary or from medicinal sources. It appears in the plasma in the ionic state as iodide, or in covalent organic form, but never as iodine. It is normally present in serum in concentrations of approximately one microgram per 100 ml. The major portion of circulating iodide is either taken up by the thyroid gland or cleared by the kidney. The remarkable ability of thyroidal acinar cells to concentrate iodide above plasma levels is referred to as trapping (fig. 1). The differential concentration of iodide between thyroid and serum (T/S gradient) is normally 20:1, but may reach ratios as high as 500:1 in hyperthyroidism. Thyroidal extraction of serum iodide requires energy and may be enzymatically mediated. This extraction process has been referred to as the thyroid pump (fig. 1). For the most part, the activity of the trapping mechanism is dependent upon thyrotropin stimulation although intrathyroidal iodide stores may in part regulate this process intrinsically.

Trapping is a critical factor in thyroid hormonal synthesis. It can be readily demonstrated in patients with hyperthyroidism (fig. 2) through inhibition by various chemical compounds of the second step in thyroid synthesis (binding). It is not easy to demonstrate this in normal subjects following administration of these drugs because of their low total radiiodide uptake. Trapped iodide may be released from the thyroid gland by thiocyanate (SCN⁻) on perchlorate (ClO₄⁻) ions in appropriate dosage. Release results from inhibition of the mechanism responsible for the maintenance of the thyroid/serum gradient, thus preventing concentration of iodide. Trapped iodide, not yet organically bound, will then diffuse from the thyroid into the plasma until the thyroid/plasma ratio reaches unity. In the absence of a thyroidal gradient, as in the patient receiving therapeutic doses of potassium perchlorate, iodide may still be made available by diffusion to the intracellular synthetic pathways, but much higher plasma levels are required to “drive” oxidative synthesis. Clinically, this is strikingly demonstrated in hyperthyroid patients rendered euthyroid by potassium perchlorate. If such patients are given large doses of iodide, as preparation for thyroidectomy, the perchlorate block will be opposed by diffusion of iodide to an extent sufficient to cause exacerbation of hyperthyroidism. Therefore, an organic goitrogen must be substituted during the interval when iodide is given.

It is of interest that a genetic variant of cretinism with goiter has been described in which there appears to be congenital absence of the trapping mechanism. Such patients
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Behave biochemically as if treated with perchlorate in that their thyroid glands fail to trap significant amounts of administered radioactive iodine. In normal patients, however, the thyroid trap functions as a reservoir to perpetuate a high concentration of intracellular iodide which is readily available for the second step in synthesis: binding.

Binding. Trapped iodide is oxidized (probably enzymatically via a peroxidase system) to a higher valence-intermediate form, the precise nature of which is uncertain. This oxidized intermediate rapidly iodinates the tyrosyl constituents of thyroglobulin (fig. 1) to form the organic compounds monoiodothyroxine (MIT) and diiodothyroxine (DIT). Once iodide is "bound" as MIT or DIT, it is no longer diffusible and cannot be discharged by perchlorate or thiocyanate ion. Thus, the term binding implies the oxidative iodination of the tyrosyl constituents in thyroglobulin to form the organic compounds MIT and DIT.

Inhibition of binding, either at the site of iodide oxidation or iodotyrosine formation, can be induced by several groups of chemical compounds. Of particular interest are the thioureylenes, such as propylthiouracil or methimazole. These goitrogenic compounds block thyroid hormonal synthesis by inhibiting formation of MIT and DIT.29 As shown in figure 2 hyperthyroid patients receiving a blocking dose of methimazole continue to trap iodide but are unable to bind it to form MIT and DIT. In such patients, the trapped iodide is dischargeable by perchlorate or thiocyanate. An interesting congenital aberration in thyroid hormonal synthesis provides the clinical counterpart of this chemically induced block to binding. These goitrous cretins are able to trap iodide at rapid rates, but are unable to form MIT or DIT.22, 23 Administration of perchlorate to these cretins permits rapid discharge of trapped iodide in a manner analogous to that shown in figure 2. An interesting subgroup of this disorder, Penred's syndrome, is associated with deafness and a partial defect of the type described.50

Coupling. Thyroglobulin is an available storage depot for the precursors of thyroid hormone, mono- and diiodothyroxine. Approximately 50 per cent of thyroidal iodine is present as the iodotyrosines in thyroglobulin. Probably under the stimulus of thyrotropin, two molecules of diiodothyrosine in thyroglobulin condense (couple) to form 3,5,3',5'-l-tetraiodothyronine, or thyroxine. Similarly, one molecule of monoiodothyroxine and one of diiodothyrosine form 3,5,3'-l-triiodothyronine (fig. 1). These metabolically active amino acids constitute the major thyroid hormones in thyroglobulin. Other detectable but probably metabolically insignificant iodinated thyronines have been reported.

The coupling of iodotyrosyl radicals to form iodothyronines is probably enzymatically controlled and sterically restricted. Not all iodotyrosyl radicals appear to be suitably contiguous in the thyroglobulin molecule to participate in this condensation. An interesting group of goitrous children with hypothyroidism demonstrate partially defective or complete absence of coupling.22, 23 A partial coupling defect in one such patient has been associated with cochlear deafness.31

Release. The complex protein, thyroglobulin, contains thyroxine and triiodothyronine, along with their iodotyrosine precursors. Consequent to stimulation by thyrotropin, proteolytic hydrolysis of thyroglobulin releases the stored iodinated amino acids (fig. 1). Thus, thyroxine and triiodothyronine are secreted into the circulation. The iodotyrosines, MIT and DIT, normally are not released into the circulation. The enzyme tyrosyl-deiodinase deiodinates iodotyrosines, but not iodothyronines. It thus prevents loss of thyroidal iodide which can be recycled and utilized for storage, or for further thyroid hormonal synthesis. Congenital absence of tissue deiodinase results in loss of iodotyrosines in the urine and reduced synthesis of thyroxine.22, 23, 22

Iodide Inhibition of Thyroidal Hormonogenesis

Knowledge concerning the action of iodide upon the chemical reactions incident to thyroid hormonal synthesis is incomplete. Attempts to develop compartmental models to explain this complex sequence of events have failed to simplify concepts of such action. However, the clinical consequences of iodide administration in hyperthyroidism are well recognized. It is of some historical interest that physicians early failed to appreciate the manner in which
Fig. 3. The effect of small doses of iodide on inhibition of binding in a patient with hyperthyroidism. This study is analogous to that in figure 2. However, in the patient above, carrier iodide 1.0 mg. was used to induce the same block as was shown following administration of methimazole. Acutely, the effects of the two agents on this step are indistinguishable. Unfortunately, this action of iodide is often incomplete and transient. Iodide also inhibits thyrotropin action on proteolysis (see text).

excess iodine, so essential to thyroid hormonal synthesis, could also inhibit formation and release of these hormones. Although familiar to ancient civilization, iodide was considered contraindicated as a treatment for goiter until reintroduced by Plummer in 1923 for therapy of hyperthyroidism. Today, the preoperative use of iodide is essential to avoid excessive glandular vascularity and friability.

Two sites of biochemical inhibition by iodide have been fairly well delineated. Through studies of secretion rate, it has been shown that the primary effect is upon the release of thyroxine and triiodothyronine from thyroglobulin. This phenomenon involves interference with the action of thyrotropin upon the proteolytic enzymes responsible for hydrolysis of thyroglobulin. It was initially suggested that iodide might act directly upon secretion or inactivation of thyrotropin, but current evidence strongly suggests inhibition of thyrotropic proteolytic action. This effect can be reversed by administration of exogenously admin-
perchlorate (fig. 3). Similar effects of iodide at this step in synthesis have been shown in other hyperplastic goiters such as those of "iodide myxedema" \(^{40, 41}\) (fig. 4) and Hashimoto's struma \(^{40, 42}\) (fig. 5). Patients with hyperthyroidism appear to be more sensitive than normals to the inhibitory effects of iodide.\(^{43}\) This response has been suggested as a diagnostic test. The action of iodide upon synthesis, like that upon release, appears to be transient and incomplete. Iodide probably acts at other sites in the production of thyroid hormones, but these remain to be clarified.

The kinetics of the biochemical reactions required for oxidative iodination of tyrosyl radicals in thyroglobulin are difficult to characterize. It seems reasonable to postulate that increasing quantities of iodide substrate produce concomitant increases in iodotyrosyl products to a limiting maximal value. Beyond this, there may be inhibition of product formation by further increase in iodide substrate. Thus, high concentrations of intrathyroidal iodide may not be efficiently handled by a rate-limiting reaction, or perhaps there may be direct inhibition of enzymatic action by high substrate concentrations. This phenomenon has been studied clinically by activation analysis for total stable iodide uptake in human thyroid glands.\(^{44}\)

**Thyroid Hormonal Transport**

Upon release into the circulation, thyroxine and triiodothyronine associate with plasma proteins to be transported to cellular destinations. The nature of the transport proteins has recently received considerable attention.\(^{45-48}\) It appears that the thyroid hormones circulate in combination with three carrier proteins. The first, interalphaglobulin, has an electrophoretic mobility between the alphone and alpha-two globulins, and has been designated TBG. The second, prealbumin, moves ahead of albumin in an electrophoretic field, and has been termed TBPA. Finally, a small fraction of thyroid hormones also travels in association with albumin as a secondary carrier. Triiodothyronine is less firmly bound than thyroxine to interalphaglobulin, and probably not at all to prealbumin. Thus, triiodothyronine disappears more rapidly from the circulation.

![Fig. 5. The inhibitory action of small doses of iodide in patient with Hashimoto's struma. As in "iodide myxedema" and hyperthyroidism, the thyroid gland in Hashimoto's struma is readily blocked by the action of small doses of carrier iodide.](image)

Thyroxine and triiodothyronine bound to protein can be readily precipitated from plasma. The amount of iodine in the protein precipitate can be determined quantitatively after suitable digestion and distillation. This measurement of serum precipitable iodine (SPI) or protein-bound iodine (PBI) reflects the combined concentrations of the two circulating thyroid hormones. In the absence of interfering iodine containing substances, this is a convenient chemical determinant of clinical thyroidal status. The normal range of serum protein-bound iodine is from 4.0 to 8.0 \(\mu\)g.\(^{100}\) ml. In the presence of increased levels of circulating inorganic iodide, the serum PBI may become factually elevated. In such instances, the butanol-extractable iodine (BEI) is useful. It is of interest that abnormal iodinated proteins may appear in the circulation in certain disorders such as one variety of goitrous cretinism\(^{22, 23}\) and in Hashimoto's struma.\(^{48}\) In these instances, the serum PBI may be increased while the BEI still provides an accurate measure of thyroid hormonal concentration. Many organic iodinated compounds spuriously elevate both the PBI and the BEI.

There is in serum an equilibrium between
hormones in the bound and in the “free” or diffusible form. It is probably the “free” form that traverses cellular membranes. Since the major portion of circulating hormones are bound to plasma proteins, variations in the binding capacities of these proteins will alter PBI and BEI levels. Certain physiologic and pathologic conditions which are not directly related to thyroid function, may influence this binding capacity and thus influence the levels of circulating bound thyroid hormones. For example, pregnancy and estrogen administration both raise thyroxine-binding globulin (TBG) capacity and thereby the PBI. Preliminary results in this laboratory indicate that norethynodrel (Enovid), presumably by virtue of its estrogenic content, induces a rise in PBI and in thyroxine binding capacity to a degree observed in normal pregnancy. Contrariwise, the PBI level is known to decline in the presence of certain drugs which lower thyroxine-binding capacities of TBG. These are listed in Table 1 and include hydantoins, androgens and some anabolic steroids. In cirrhosis of the liver and in nephrosis, the PBI may also be low. The mechanism of such decreases is unknown but may result from alterations in the binding capacities of thyroxine-binding proteins. Large doses of salicylates are reported to decrease serum PBI by decreasing the binding capacity of TBPA. It is worthwhile to point out in such instances, that the “free” or available thyroid hormones probably remain unchanged. For example, in normal pregnancy, the serum PBI rises, presumably as a result of estrogenic effect, but “free” thyroxine remains in the normal range and the patient is euthyroid. Similarly, hydantoins and androgens do not influence clinical thyroidal status.

A helpful laboratory test for measurement of thyroid binding capacity has recently been introduced by Hamolsky. This red cell uptake test (RBC-T3) is based upon the observation that red blood cells in the circulation, and in vitro, bind triiodothyronine. The degree of binding in vitro is inversely proportional to that fraction bound to the plasma proteins (mostly TBG in the case of triiodothyronine). The degree of binding to red cells has been found to be increased in hyperthyroid patients whose protein binding sites are relatively saturated. Conversely, the RBC-T3 test is decreased in hypothyroid patients, and during normal pregnancy. The normal range of values for the RBC-T3 test are tabulated in Table 2, for various clinical states. Further detailed review of the laboratory tests available for the diagnosis of thyroidal disorders is beyond the scope of this article. The reader is referred to several textbooks which fully cover this important subject.

**Preoperative Management of Hyperthyroidism**

The application of chemical compounds to the therapy of hyperthyroidism is a milestone in the evolution of the clinical pharmacology of endocrine disorders. Detailed reports of the use of antithyroid compounds for long-term management and for preoperative preparation are available. Various preparative regimens have been proposed; each has its proponents. In our experience, a program which has been particularly successful is the use of combined antithyroid and thyroid therapy. This offers a safe, effective and relatively simple means of inducing euthyroidism. In general, hyperthyroid patients are started on propylthiouracil 100 mg. (or methimazole 10 mg.) by mouth every six to eight hours. Patients with diffuse goiter usually show marked improvement in six to eight weeks. When it is evident that the patient is approaching euthyroidism as indicated by edema-free weight gain, slowing of the pulse rate, and subjective symptomatic improvement, USP thyroid in daily doses of 120 mg. is added to the regimen. This dose of thyroid can be increased later to 180 mg. daily if the goiter is initially large, or if ophthalmopathy is severe and if tolerated by the patient.
Combined antithyroid-thyroid therapy has several distinct advantages. It obviates any hypothyroidism which may result from excessive action of antithyroid medication while allowing full use of blocking doses of these compounds. In this regard, it is noteworthy that hypothyroidism is undesirable, particularly in preparation for thyroidectomy, in that it alters responsiveness to drugs and anesthetics, delays healing and convalescence, and adversely affects ophthalmopathy. Full replacement doses of thyroid inhibit the goitrogenic effect of antithyroid compounds and thus produce a smaller, less hyperplastic and more compact thyroid gland. Moreover, thyroid is of benefit in stabilization of the ophthalmopathy in such a program. A further benefit is the protection afforded if pregnancy occurs during treatment. The thyroid administered under these circumstances prevents goiter and hypothyroidism in the fetus which results from placental passage of antithyroid compounds.

Following full restoration to euthyroidism on this regimen, it is wise to allow ample time for restitution of the catabolic consequences of this disorder. When fully accomplished, usually four to six months after initiation of therapy, elective thyroidectomy may be scheduled. At this time, it is desirable to start Lugol's solution or saturated solution of potassium iodide in doses of 0.5 ml. t.i.d., with meals, for the involutional effect on the thyroid gland. Treatment with iodide for 10 days prior to operation is sufficient to reduce hyperplasia and vascularity, and to provide a satisfactory surgical status of the thyroid gland. While some physicians still cling tenaciously to tradition, the modern medical management of hyperthyroidism has no place for use of iodides alone, to induce euthyroidism. The use of iodides is often incomplete, the effect transient and unreliable, and should be relegated to a place of historical interest only. In patients sensitive to the available antithyroid medications, radioactive iodine provides a safe and effective alternative therapy.

Of particular importance and worthy of emphatic repetition is the dictum that subtotal thyroidectomy must be an elective procedure, performed under optimal circumstances with the patient fully euthyroid. With the availability of alternative therapy, operation need not be undertaken when the risk is greater than in thyroidectomy for non-toxic goiter. Indeed, if complications mitigate against safe surgical management, other therapy such as radioactive iodine or long-term antithyroid drugs should be employed. With proper selection of patients, surgical complications will be minimal and the results gratifying to all.

Patients receiving antithyroid compounds should be advised of possible toxic reactions. The physician must exercise good judgment in the handling of such complications when they occur. Fortunately, serious toxic reactions are not common, particularly when these drugs are used for relatively short periods of time and in moderate dosage. Skin rash constitutes the commonest toxic manifestation. It is usually not severe nor of an exfoliative character. Of more serious import are suppressive actions of antithyroid compounds on myogenesis. It is not generally appreciated that untreated hyperthyroidism may be associated with an absolute reduction in the number of polymorphonuclear leukocytes, resulting in a mild leukopenia and a relative lymphocytosis. Antithyroid compounds often exaggerate this leukopenia by further reduction in circulating polymorphonuclear leukocytes. This effect appears to be dose-related. When moderate in degree, it will often correct itself or respond to modest reduction in dosage. A "rule of thumb" has been that a patient on medication should be carefully followed when the total polymorphonuclear leukocyte count remains above 1,500 per cubic millimeter. Below this critical level, the antithyroid compound should be discontinued and other therapy undertaken.

In patients with diffuse goiter, failure of antithyroid compounds to induce euthyroidism in two to three months often results either

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<th>Clinical State</th>
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from failure of the patient to take his medication or from insufficient dosage. With multinodular goiters, the response may be less rapid or require larger doses, sometimes double those employed for diffusely enlarged glands. Several more extensive reviews of the pharmacology of antithyroid compounds have recently appeared. 5, 66

Preparation of the patient for subtotal thyroidectomy is often facilitated by attention to adjunctive measures in addition to those directed at reduction in metabolic rate. These include limitation of physical activity, use of a high protein, nutritionally balanced diet with supplemental B-complex vitamins, and regulation of any complicating disorders such as diabetes, hypertension or congestive heart failure. Attention to emotional support and reassurance is of great importance. Sedation is often beneficial. The judicious use of barbiturates is usually adequate to alleviate the anxiety associated with hyperthyroidism. Reserpine has recently gained vogue and, indeed, when used in sufficient dosage may decrease tachycardia and afford a degree of tranquilization without somnolence. Adverse effects with large doses of this alkaloid are not uncommon. Some patients are said to develop unexpected hypotension during anesthesia as a result of depletion of tissue catecholamines. 57 This complication should be anticipated by the anesthesiologist.

The presence, course, or severity of the ophthalmic involvement in hyperthyroidism does not necessarily parallel that of the metabolic state. Indeed, exophthalmos may antecede, accompany or follow the onset of hyperthyroidism. It may improve, remain static or progress following effective therapy. It is an improved, but clinically evident observation that rapid correction of the thyrotoxic state may initiate, exacerbate or cause progression of exophthalmos and ophthalmopathy, particularly if hypothyroidism ensues. Care of the proptotic, photosensitive, and myopathic eye is of the utmost importance. Preservation of the corneal epithelium to prevent ulceration and subsequent opacification is critical; efforts at prophylaxis require skill, persistence and patience on the part of both physician and patient. Ablative procedures such as subtotal thyroidectomy or radioactive iodine therapy may adversely affect severe forms of thyroplastic exophthalmos, particularly if performed during an active, progressive phase. For this reason, conservative management with anti-thyroid compounds and thyroid substitutional therapy provides the most effective and least noxious therapy when severe progressive ophthalmopathy is present. As a rule, ablative procedures should be delayed until ophthalmopathy has become stabilized and controlled. Once the malignant phase has evolved, arrest of progression becomes difficult and hazardous.

Measures directed toward the care and protection of the eyes before, during and after thyroidectomy are vital if significant exophthalmos or conjunctival suffusion exist. Such simple expedients as taping the lids shut, use of head blocks during sleep, wearing tinted spectacles, instillation of methylcellulose drops or boric acid ointment, and at times lateral tarsorrhaphy are of assistance. It should be remembered that exophthalmic patients may be unable to close the eyelids during sleep or anesthesia and in such instances, deliberate closure to protect the corneas is mandatory.

Anesthetic and Surgical Considerations

Advances in the techniques of preanesthetic preparation and the conduct of anesthesia have vastly improved both the morbidity and mortality following thyroidectomy. However, there are still technical difficulties inherent in the excision of certain glands. The presence of an extremely large goiter, particularly one with intrathoracic extension often necessitates a more extensive surgical procedure. Thyroidectomy similarly is more difficult in patients with recurrent hyperthyroidism following previous excision. It is usually advisable for such patients to receive radioiodine since the complications following multiple thyroidectomies are markedly increased. Patients prepared exclusively with an antithyroid compound, without the addition of iodides preoperatively, exhibit excessive hyperplasia and vascularity thus constituting an unjustifiable hazard. Fortunately, experience gained the past forty years has prepared the skillful surgeon for the exigencies of this procedure.

Evaluation and discussion of such problems as selection of anesthetic agent or procedure, the relative value of tracheal intubation, posi-
tioni of the patient and preservation of cardiopulmonary function are beyond the scope of this presentation. The interested reader is referred to current reviews of these and associated matters.68, 69

The complications of thyroid surgery 70 fall largely into seven groups:

1. Hemorrhage
2. Respiratory obstruction
3. Hypoparathyroidism
4. Thyroid storm
5. Hypothyroidism
6. Progressive exophthalmos
7. Persistent hyperthyroidism

**Hemorrhage**

Massive hemorrhage during thyroidectomy, is fortunately rare with adequate exposure and careful identification of anatomic landmarks. Venous hemorrhage may result from avulsion or division of one of the lateral lobes, less frequently, the internal jugular vein. Other veins rarely present difficulty unless the gland extends into the superior mediastinum. Laceration of an inferior thyroidal vein subterminally may lead to bleeding into the superior mediastinum where control becomes a problem. It must be emphasized that commonly the most dangerous hemorrhage follows completion of operation. This must be anticipated even after the most uneventful procedure since it may occur up to two or three days postoperatively. Hemorrhage may arise in the recovery room especially if the patient emerges from anesthesia coughing, straining or vomiting. The resultant rise in venous pressure may dislodge ligatures or permit bleeding from relatively small vessels. Venous bleeding is frequently more insidious than arterial, but hemorrhage from a large vein may produce rapid onset of dramatic symptoms. Forceful bleeding, particularly from the superior thyroidal artery may produce laryngeal and tracheal obstruction with acute cervical tumor, anxiety, dyspnea and laryngeal stridor. Decisive and rapid action is essential to avert death. If detected early, there is usually sufficient time to return the patient to the operating room for hemostasis. Immediate opening of the cervical incision for decompression at the bedside is required when tracheal obstruction is severe.

With moderate bleeding, there is often the temptation to temporize. Evacuation of clots beneath the flap, application of pressure dressings, and insertion of drains may delay but should not be substituted for adequate hemostasis. In the operating room, with careful exposure, control of the bleeding can be readily accomplished. On rare occasions, coagulation defects, platelet insufficiency or capillary abnormalities require special diagnostic measures and specific treatment.

**Respiratory Obstruction**

Tracheal compression from massive hemorrhage is not the only cause of laryngeal obstruction. It may result from laryngeal edema or follow paralysis of one or both recurrent laryngeal nerves. Stridor from injury or severance of the nerve is usually apparent following operation upon extubation of the trachea. It may be partial or transient but requires careful observation. Damage to both recurrent nerves is rare when thyroidectomy is performed for hyperthyroidism. However as in other causes of significant laryngeal obstruction, it is an indication for immediate tracheotomy. It is wise to examine the vocal cords carefully before as well as after thyroidectomy.

**Hypoparathyroidism**

Variation in the number and position of the parathyroid glands as well as difficulty in their identification at operation have made it virtually impossible to reduce the prevailing incidence of hypoparathyroid tetany postoperatively. The recorded incidence of this complication varies in different series; the usual figure is given as one per cent. In some series where hypocalcemia was sought by determination of serum calcium levels following each operation, many mild and transient cases were detected. In such reports the overall incidence of hypoparathyroidism following thyroidectomy for hyperthyroidism was 2.9 per cent. It was 2.02 per cent for diffuse goiter with hyperthyroidism, 2.28 per cent for toxic adenomatous goiter and 9.5 per cent after a second operation for recurrent hyperthyroidism. It must be emphasized that this
distressing complication is frequently only temporary. The onset may take place at any time between the first and sixth postoperative days. Not infrequently, however, it makes an appearance acutely in the recovery room and here may become the responsibility of the anesthesiologist. Implantation of excised parathyroid tissue if recognized at the time of operation can be of value in preventing tetanic episodes.\textsuperscript{71}

The major clinical manifestation of hypoparathyroidism is tetany. Hypocalcemia and the resultant increased neuromuscular excitability are the precipitating factors. Tetany is associated with a decrease in the urinary excretion of phosphorus, a rise in the level of serum inorganic phosphorus, a fall in the serum calcium and a decrease in the urinary excretion of calcium. When serum calcium levels fall below a critical value of from 7 to 8 mg. per cent (3.5 to 4.0 mEq./100 ml.), signs and symptoms of tetany become evident. In this regard, it must be remembered that tetany may be aggravated by alkalosis or alleviated by acidosis.

The earliest manifestations of tetany are nervousness, restlessness and perioral paraesthesias with numbness and cramps in the extremities. These premonitory symptoms are soon followed by carpopedal spasm, laryngeal stridor and generalized convulsions with spasm of both voluntary and involuntary muscles. Tachycardia, irregularities in cardiac rhythm and prolongation of the Q-T interval on the electrocardiogram reflect the hypocalcemic effects upon the myocardium. Abdominal pain, nausea and vomiting attest to involvement of the musculature of the gastrointestinal tract. Tetany may be latent at serum calcium levels from 7.0 to 8.0 mg. per cent. Several useful tests to detect occult tetany have been described. Chvostek's sign is elicited by tapping the trunk of the facial nerve just anterior to the external auditory meatus. A faintly positive sign consists of contraction of the muscles of the upper lip on the tapped side; contractions of the alae nasi, eyelid and of the muscles of the face suggest more profound tetany. Trousseau's sign is sought by inflating a blood pressure cuff to a level that occludes the arterial circulation to an extremity for at least three minutes. A positive sign is the appearance of carpopedal spasm.

The intravenous infusion of calcium salts in tetany can be lifesaving. Calcium gluconate in doses of from 10 to 20 ml. of a 10 per cent solution is usually employed. Repeated intravenous infusions frequently prove necessary if symptoms recur before oral therapy can be initiated. The need for continuation of therapy must be carefully determined for each patient through evaluation of the clinical state and from serial laboratory determinations of serum calcium and phosphorus. Following correction of tetany, oral therapy may be instituted where required. Calcium chloride solutions by mouth can be used for brief periods along with supplemental aluminum hydroxide compounds (phosphate-free) to facilitate absorption of calcium by precipitation of intestinal phosphates. The dosage and frequency of administration such medication must be individually determined. Adequate therapy controls the symptoms of tetany. However, control of the overt symptoms may obscure borderline values of serum calcium and permit cataract formation. For this and other reasons, persistent and prolonged hypocalcemia must be regulated on the basis of repeated determinations of serum calcium.

The therapy of chronic hypoparathyroidism requires constant and meticulous attention to details and should never be treated casually. This difficult and trying complication is discussed more fully elsewhere in this symposium and in several recent articles.\textsuperscript{71, 72} Only a few generalizations merit emphasis here: (1) Correction of hypothyroidism, if co-existent, is beneficial through improvement of calcium homeostasis in patients with hypoparathyroidism. (2) There may be neuromuscular "adaptation" to hypoparathyroidism with spontaneous disappearance of tetany but accurate determinations of serum calcium must be performed to obviate cataract formation secondary to persistent mild hypocalcemia. (3) Vitamin D therapy may increase the renal clearance of calcium with the paradoxical appearance of hypercalciuria in the presence of hypocalcemia, necessitating a high oral water intake to prevent renal calcinosi or calculi. (4) Titration of the optimal dose of vitamin D may be difficult particularly with fluctuating
responsiveness, and because of the unreliability of urinary calcium determination in reflecting serum calcium levels. Until there is a return of endogenous parathyroid function or until the patient’s parathyroid status has been adequately characterized, the serial determination of serum calcium levels is of the utmost importance in preventing symptoms and complications.

From this discussion of the three mentioned postoperative complications, it is apparent that continuous postoperative surveillance is essential in patients undergoing thyroidectomy. The frightening occurrence of a tetanic crisis or airway obstructed by an expanding hematoma should be anticipated and vigorously treated. At an unexpected time, the presence of a small bedside kit containing a vial of calcium gluconate and an emergency tracheotomy set may avert these disastrous consequences.

THYROID STORM

Probably one of the most feared complications of thyroidectomy is the so-called thyroid storm. Once experienced, this catastrophe remains deeply engraved in the mind of the physician. In the past, thyroid storm usually occurred postoperatively following inadequate restoration to euthyroidism. Fortunately, appropriate use of antithyroid drugs permits full correction of the hypermetabolic state before operation and such crises are now quite rare. Physiologically, this complication may be viewed as a decompensated state of hyperthyroidism precipitated by the excessive release into the circulation of thyroid hormones during operative manipulation of the poorly prepared thyroid gland. The striking features usually become manifest 24 to 72 hours postoperatively with rapid, forceful sinus tachycardia or auricular fibrillation, nausea, vomiting, diarrhea, dehydration and tachypnea. At times severe thermal instability may supervene with fever rising to 107°F; at times hypothermic shock may occur. There is often marked agitation with restlessness, delirium and prostration. This frightening complex of events may simulate adrenocortical insufficiency. Indeed, there is evidence to suggest limited adrenocortical reserves in hyperthyroid patients. Hepatic function, often mildly impaired in severe hyperthyroidism, may progress to decompensation with severe jaundice and hepatic coma. Such a chaotic event as thyroid storm does not arise from a trivial insult in some mysterious, unpredictable fashion as implied in the earlier literature. The rarity of this complication in patients properly selected and adequately prepared for operation attests to its nature as a metabolic catastrophe resulting from the rapid recrudescence of hyperthyroidism during or following surgery.

The physician may at times be perplexed by the unexpected finding, post-thyroidectomy, of fever, tachycardia, tachypnea and leukocytosis of obscure origin. With the knowledge that the patient was fully euthyroid at the time of the operation, causes other than “storm” should be carefully excluded. The most common of these is infection. What appears to be an innocuous wound may, upon removal of a skin suture, surprise the sceptical observer through release of pus and relief of the most uncomfortable patient. Such postoperative complications as septicemia, atelectasis, pneumonitis, pulmonary embolism, congestive heart failure or urinary tract infection may mimic thyroid storm. It is a good policy not to accept a diagnosis of postoperative storm until all conceivable causes of sepsis or the other complications have been excluded.

In the event of the rare occurrence of thyroid storm, therapy must be applied to the particular systems most critically involved. There is no therapeutic means of removing or inhibiting the action thyroid hormones once released into the circulation. For this reason, prompt attention must be directed toward alleviation of fever if above 103–104°F, tachycardia if above 140–150, and congestive heart failure or shock if present. Although use of iodiodes intravenously has had a great vogue, there is no clear evidence that such therapy in any manner inhibits the extrathyroidal action of thyroid hormones. Indeed, the high mortality rate following thyroid storm, despite widespread use of large doses of iodiodes, attests to their low therapeutic value once storm has occurred. Propylthiouracil in doses from 150 to 200 mg. every six hours should be given to block further hormonal synthesis and iodiodes then given to inhibit further secretion of stored hormone. Intravenous glucocorticoids, such as hydro-
cortisone hemisuccinate may be given in large dosage initially followed by a constant, slow infusion. Use of oxygen, particularly in a humidified, cooled enclosure is beneficial. Sedation with barbiturates or, in the absence of delirium, reserpine alkaloids, phenothiazine derivatives or morphine may be helpful in allaying anxiety. Such simple measures as hydration, correction of electrolyte disturbances and reassurance are necessary adjuncts.

The anesthesiologist is at times able to perceive a foreboding of an operative difficulty when the patient evinces tachycardia, excessive warmth and taehynpnea prior to induction of anesthesia. When there is any doubt as to the feasibility of approaching thyroid surgery because of suspicion of hyperthyroidism, it is wise to postpone operation and re-assess the situation, rather than to proceed hesitatingly.

**Hypothyroidism**

The signs and symptoms of thyroid deficiency can be noted as early as the first few weeks postoperatively. At times, hypothyroidism occurs insidiously and is not detected until a period of from one to five years has elapsed. In most reported series, no definite relationship has been established between the development of postoperative myxedema and (1) the degree of hyperthyroidism; (2) duration of antithyroid treatment; (3) duration of the disease; or, (4) weight of the goitrous tissue removed. The manifestations and treatment are well known. Since recent advances in this area have been fully described elsewhere, a detailed discussion of this topic is beyond the scope of this review.

**Progressive Exophthalmos**

The recognition and treatment of this disorder has already been mentioned. A mild degree of exophthalmos, if stable, is not in itself a contraindication to thyroidectomy. However, in the presence of significant ophthalmopathy, it is prudent practice to institute or to continue thyroidal substitution therapy, 120 to 180 mg, daily, prior to and for at least a year following surgery. This has several advantages: hypothyroidism is obviated during the re-adjustment period; it appears to stabilize any tendency to progression of ophthalmopathy; and it provides a convenient means of evaluating the activity of the remaining thyroid remnants. This latter prognostic device, the “Suppression Test,” is quite useful in determining the possibility of recurrence of hyperthyroidism following subtotal thyroidectomy, radioactive iodine or antithyroid therapy. Thus, in a patient receiving 120 to 180 mg. USP thyroid for two weeks or more, a 24-hour radioactive iodine uptake greater than 20 per cent is strongly suggestive of impending or future recurrence.

**Persistent Hyperthyroidism**

Finally, there is the uncommon result which is most distressing after thyroidectomy: persistence of hyperthyroidism despite what is deemed a more than adequate removal of thyroid tissue. Abwood made the provocative observation that ablative procedures do not “cure” hyperthyroidism, but merely reduce the quantity of gland available for production of thyroid hormones. The thyroid “remnant” may remain abnormal for years despite clinical euthyroidism. It is surprising, but probably valid, that beyond a critical point, the actual quantity of tissue removed does not necessarily guarantee a satisfactory result. Goode performed total thyroidectomies and found the recurrence rate no less than that following subtotal excision. In the event of persistent or recurrent hyperthyroidism, the most expedient and least detrimental therapy is the use of radioactive iodine. As already noted, re-operation is associated with a high incidence of complications such as tetany and laryngeal nerve injury, as well as an increased rate of recurrence.

**Summary**

Some basic considerations in the treatment and operative management of hyperthyroidism have been described. Intelligent therapy entails a thorough knowledge of the chemical synthesis, secretion, transport and physiologic actions of thyroid hormones. The critical importance of performing thyroidectomy only after the patient has been rendered fully euthyroid has been emphasized. A convenient and effective program which provides a balanced regimen for hyperthyroidism is described. This entails combined use of antithyroid drugs with full replacement doses of
desiccated thyroid. The addition of iodine is reserved exclusively for the ten-day-period before operation.

Antithyroid drugs and radioactive iodine currently provide excellent alternative modes of therapy for hyperthyroidism. Subtotal thyroidectomy, therefore, must now be considered a purely elective treatment for selected individuals. Under such circumstances, the conduct of anesthesia should not differ significantly from that required for surgical excision of non-toxic goiter. Management of complicating features of thyroidectomy such as hemorrhage, respiratory obstruction, hypoparathyroidism, thyroid storm, hypothyroidism, malignant exophthalmos and persistence of hyperthyroidism has likewise been discussed. In properly selected and judiciously prepared patients, subtotal thyroidectomy provides a safe and reliable therapy for hyperthyroidism with gratifying results both for the patient and for the physician.

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References


**SCLERODERMA** Of thirteen patients with systemic scleroderma six patients were dyspneic and six had evidence of pulmonary fibrosis. All had low vital capacity and decreased compliance and twelve had low diffusing capacity. Maximal breathing capacity and timed vital capacity were normal. These changes are characteristic of the "alveolar-capillary block" syndrome. The incidence of pulmonary involvement is much higher when tested objectively than from clinical appraisal. Pulmonary fibrosis is much more prevalent at post mortem than on roentgenogram. The "hidebound" chest may contribute to impairment of pulmonary function, but its effects are probably much less important than those of interstitial fibrosis. (Adhirikari, P. K., and others: Pulmonary Function in Scleroderma, Amer. Rev. Resp. Dis. 86: 823 (Dec.) 1962.)