

# THYROID TODAY

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## MANAGEMENT OF THE PATIENT WITH GRAVES' OPHTHALMOPATHY

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Ophthalmopathy of Graves' disease is a disorder of unknown etiology and highly variable clinical presentation, which may accompany, precede, or follow hyperthyroidism. It may require no treatment at all or may demand a series of aggressive therapeutic maneuvers, including high dose corticosteroids or a variety of aggressive surgical procedures. Because the condition in its more severe forms is uncommon (2 to 3% of hyperthyroid patients), few practicing physicians gain extensive experience with it. This review, which is based on personal experience with more than 500 patients with ophthalmopathy examined over the last ten years, will present some current concepts of etiology, explore the variants in presentation, discuss differential diagnosis and emphasize selection of the best treatment alternatives.

### Pathology

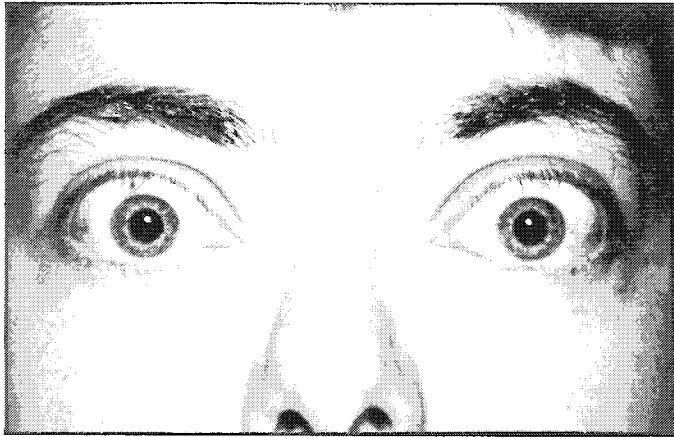
To understand the clinical features of Graves' ophthalmopathy, a few anatomic features of the orbit should be kept in mind. The position of the eye is quite simply determined by the amount of the orbital tissues and the extent to which they fill the orbital cavity. In Graves' ophthalmopathy, retrobulbar and eye muscle fat increase markedly. Rundle and Pochin<sup>1</sup> have shown that protrusion of the eye by one millimeter results from an increase in bulk of orbital tissue of 0.67 cc assuming a specific gravity of 0.96 and a mean orbital volume of 26.1 cc. It follows that a considerable exophthalmos of 6 mm will be caused by a bulk increase of only 4 cc. Deposition of mucopolysaccharides,

primarily hyaluronic acid in the intercellular ground substance, adds to the orbital congestion since hyaluronic acid has a marked propensity to bind water. Fatty infiltration in the extraocular muscles markedly increases their bulk up to eight times their normal size and eventually is followed by fibrosis and impairment of their function. The congested orbit is manifest anteriorly by prominence of the conjunctival vessels and conjunctival edema. The upper eyelid, which may be retracted in the thyrotoxic stage due to sympathetic overactivity, may remain persistently retracted due to fatty infiltration first and then fibrosis of the levator. Because lower eyelid anatomy is now understood much more clearly thanks to the work of Callahan, Beard, and Quickert, it is known that the retractor of the lower lid may be similarly affected. The clinical presentations of Graves' ophthalmopathy can now be logically anticipated.

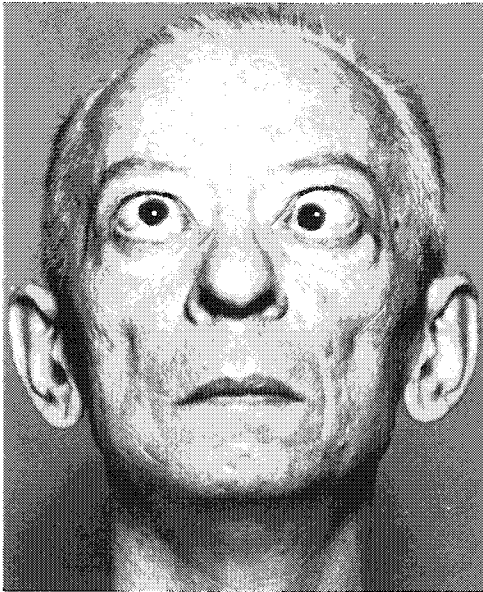
### Clinical Characteristics

Noninfiltrative ophthalmopathy is characterized by altered appearance due to eyelid retraction and is related to excess sympathetic tone as a feature of thyroid overactivity. Eyelid retraction may be seen any time serum thyroid hormone levels are raised, whether it be from administration of thyroxine or triiodothyronine, solitary toxic adenoma, toxic multinodular goiter, or Graves' disease.

Infiltrative ophthalmopathy, which is pathognomonic of Graves' disease (Fig. 1), may include eyelid retraction as one feature, but in addition soft tissue swelling, eye muscle involvement or proptosis are present to some extent. Pa-



a.



b.



c.

**Fig. 1—Variations in Expression of Graves' Ophthalmopathy.**

- a. This patient has predominantly proptosis and lid retraction.
- b. In addition to proptosis and lid retraction, extraocular muscle involvement is present.
- c. Severe inflammatory changes manifest mainly by chemosis, injection, and periorbital edema.

tients with infiltrative ophthalmopathy may complain of eye pain, lachrimation, photophobia, blurring of vision, or double vision and may exhibit findings of lid edema, conjunctival edema (chemosis), scleral injection, lid lag, globe lag, lid retraction, proptosis, exposure keratitis, corneal ulceration, papilledema, visual field scotomata and impairment of extraocular muscle function. When patients complain of blurred vision, it is important to determine if they are referring to the momentary blur which is due to lachrimation, to the intermittent blurring which is noted only when both eyes are open together and which is caused by impairment of extraocular muscle function with imperfect fusion of the images from each eye, or to the persistent and often progressive blurring of vision which is unaffected by closing one eye and which indicates either optic nerve compression or corneal edema or ulceration.

**Cause of Exophthalmos**

When long acting thyroid stimulator (LATS) was found in the serum of patients with Graves' disease in 1956 it represented a breakthrough in investigation of the disease. LATS was found in the serum of patients with Graves' disease, some of their asymptomatic relatives, and in some patients with Hashimoto's thyroiditis. Since some patients with Hashimoto's thyroiditis exhibit Graves' ophthalmopathy, this did not seem anomalous. LATS was found to bind to receptors on the plasma membrane of thyroid cells. It exerted its primary effect by stimulating thyroid adenylate cyclase and was believed to occupy the same binding site as thyroid-stimulating hormone (TSH). LATS was measured by a bioassay which depended on demonstrating a delayed release of labeled hormone release from the mouse thyroid as compared to the action of TSH. LATS, an IgG antibody, was shown to be only one of a family of thyroid stimulators which are referred to under the general term of thyroid stimulating immunoglobulins (TSI).<sup>2</sup> One of these substances, LATS protector, does not stimulate the mouse thyroid as does LATS but is active in human thyroid tissue where it competes with LATS for binding sites and thus protects LATS from neutralization. Of 50 patients with diffuse toxic goiter studied by Adams et al.,<sup>3</sup> 30 had LATS protector only, 15 had LATS and LATS protector, and 5 had neither. Infiltrative ophthalmopathy was less common in patients with LATS protector only (40%) than in patients with both LATS and LATS protector (67%).

Although LATS protector may explain the hyperthyroidism of Graves' disease, at present neither LATS nor LATS protector are considered to explain adequately the origin of Graves' ophthalmopathy, and recently Kohn and Winand<sup>4</sup> have reawakened interest in a third substance, exophthalmic producing substance (EPS), as the possible culprit. EPS is of pituitary origin and can cause proptosis

when injected into the Atlantic minnow. Kohn and Winand have shown that a fragment of the TSH molecule consisting of the beta chain and a 6000 molecular weight segment of the alpha chain contains exophthalmic activity in the mouse Harderian gland assay. These authors propose that EPS binds specifically to membrane receptors in the retro-orbital tissues and suggest that binding is enhanced by an abnormal immunoglobulin. Unfortunately, for this theory TSH is suppressed in patients with Graves' ophthalmopathy, and measurements of the alpha and beta chains separately are also low. So at present, EPS cannot be said to be the cause of Graves' ophthalmopathy.

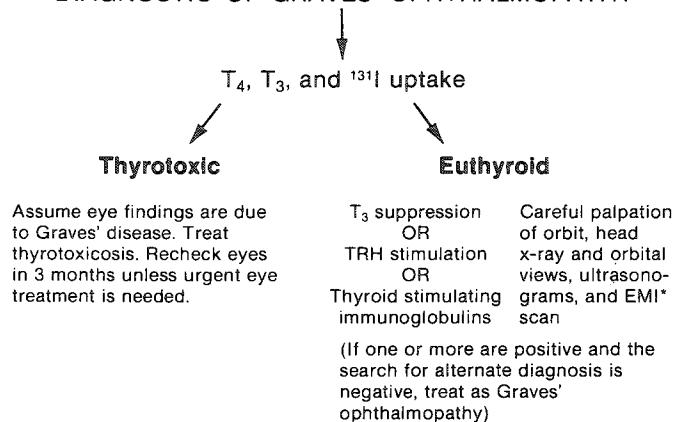
Kriss et al.<sup>5</sup> have proposed an alternative theory of the origin of Graves' ophthalmopathy. According to this view, thyroglobulin is continuously leaked from hyperplastic acini of the thyroid into lymphatics which drain to cervical lymph nodes where antibodies to thyroglobulin are rapidly synthesized. Since a direct lymphatic connection between cervical nodes and the orbit has been shown to exist, thyroglobulin (Tg), antithyroglobulin antibody (Ab), and Tg-Ab complex may be routed to the orbit where Tg binds to extraocular muscles. This binding is enhanced by the presence of the antibody. Once Tg-Ab complexes are formed on the muscles, a series of immunological events occurs which results in muscle cell injury and is followed by fibrosis and impairment of function. An attractive feature of this theory is the potential to explain asymmetrical exophthalmos based on variations between the right and left sides in the direct lymphatic flow from thyroid to orbit.

### Diagnosis

When the presenting picture is typical and one encounters a thyrotoxic patient with bilateral symmetrical eye involvement including lid retraction, lid lag, proptosis, chemosis, and restriction of extraocular muscle motion, then the diagnosis is self-evident. When the patient is euthyroid, the involvement is unilateral and fewer of the characteristic findings are present, then the diagnosis becomes increasingly difficult (Table I). Under these circumstances, clinicians rely on an unconstitutional premise—guilt by association—and diagnostic evaluation takes three separate avenues. The first is to confirm that the eye findings are consistent with Graves' ophthalmopathy, the second is to exclude the presence of any other process such as an orbital tumor which may at times mimic Graves' ophthalmopathy, and the third step is to demonstrate some evidence of a disorder in thyroid regulation. The three tests used for this purpose are the T<sub>3</sub> suppression test, the thyrotropin-releasing hormone (TRH) stimulation test, and the detection in serum of a thyroid stimulating immunoglobulin (LATS or LATS protector). Each of these tests examines for a different abnormality. The T<sub>3</sub> suppression test checks to see whether the thyroid is normally regulated by pituitary TSH, the TRH stimulation test checks for subtle degrees of hyperthyroidism not apparent in routine tests, and the serum assays for abnormal thyroid stimulators search for the substances which confirm the presence of the Graves' diathesis. Even using this constellation of testing procedures, Solomon et al.<sup>6</sup> have recently described a subset of patients with apparently characteristic Graves' ophthalmopathy who have no detectable abnormality in thyroid

TABLE I

DIAGNOSTIC FLOW SHEET FOR PATIENTS WITH OCULAR FINDINGS SUGGESTIVE OF BUT NOT DIAGNOSTIC OF GRAVES' OPHTHALMOPATHY



\*Not to be implied that every patient with Graves' ophthalmopathy who is euthyroid should have an EMI scan. In selected patients where a serious possibility of retrobulbar tumor exists, it may be a very helpful adjunct.

function or regulation and who have no abnormal stimulators in their blood. These patients remain unclassified at present but may have either "isolated Graves' ophthalmopathy" as the authors propose or pseudotumors of the orbit, which are occasionally bilateral.

## Treatment

Treatment for the most common problems is outlined in Table II. In selecting a treatment it is important to consider the following:

1. Is the patient thyrotoxic, euthyroid, or myxedematous? Correction of hyperthyroidism may correct minor eye findings of stare, lid lag, and lid retraction and correction of hypothyroidism can improve periorbital edema.
2. Where is the patient in the evolutionary pattern of the disease? Most patients with Graves' ophthalmopathy go through a period of initial worsening, then a plateau of variable length, and finally spontaneous improvement. If the patient is in the worsening phase, then follow much more closely. If spontaneous improvement is occurring, withhold the more vigorous forms of treatment such as surgery or high dose steroids.
3. What are the specific threats to function? Is the main risk from corneal exposure, from eye muscle involvement, or from optic nerve pressure?
4. What is the specific symptom most worrisome and annoying to the patient? Many patients relieved of the fear of losing vision are ready to accept surprising degrees of cosmetic change.
5. What treatment measures are best adapted to preserving vision, restoring appearance, and improving comfort?
6. To what degree have you gained the patient's informed support of the treatment alternatives you propose? These patients have many questions and fears—a lengthy discussion of the variations in course and the relationship to thyrotoxicosis in the early stages will do a great deal to maintain your rapport if the condition worsens later. It also has the advantage of removing from the patient's mind any lingering suspicion that if they have developed ophthalmopathy years after treatment of their hyperthyroidism, this means their hyperthyroidism was somehow incorrectly treated.

Some of the advances in treatment deserve special comment. Our experience with supervoltage radiotherapy has been limited and unfavorable although others have reported good results.

Retrobulbar steroids are inconvenient to administer, need to be given at least once weekly, will accomplish about as much as do systemic steroids and do not evoke systemic steroid side effects. Patients tend to tire of the repeated retrobulbar injections, and when the injections are discontinued, many patients relapse.

Systemic steroids will effectively control the optic neuropathy and inflammatory changes of ophthalmopathy, but often only at very high dosage and at the expense of eventually unacceptable steroid side effects. For such patients, transantral orbital decompression is an effective treatment.

Transantral decompression appears to be as effective as the much more extensive transfrontal procedure, but about one-third of the patients have diplopia after transantral decompression which requires an additional surgical procedure to correct it (Table III) (Fig. 2).

TABLE II

TREATMENT*	
Eye Problem	Management
Periorbital and lid edema	Elevate head of bed Don't sleep prone Use diuretics
Gritty sandy sensation in eyes Eyelids close normally	1% methylcellulose eye drops p.r.n.
Faulty coverage of globe due to eyelid retraction	Section of Müller's muscle Scleral graft insertion in eyelids Tarsorrhaphy
Intermittent diplopia	Observe Check refraction and Lancaster red/green test Consider prisms
Persistent diplopia	Extraocular muscle surgery with or without preliminary decompression
Severe inflammatory changes (injection, chemosis, pain)	Systemic or retrobulbar steroids If unresponsive to reasonable dose, transantral decompression
Severe proptosis Optic neuropathy	TRANSANTRAL ORBITAL DECOMPRESSION
**Corneal ulceration due to proptosis Severe eye discomfort particularly if unresponsive to reasonable steroid dose	or in some centers supervoltage x-ray therapy

\*It is assumed that any disorder of thyroid function will be simultaneously corrected

\*\*Combined with local measures to protect the cornea

**TABLE III\***

**SUMMARY COMPARISON OF TRANSANTRAL  
VERSUS TRANSFRONTAL DECOMPRESSION**

ASPECT	TRANSANTRAL DECOMPRESSION	TRANSFRONTAL DECOMPRESSION
Restoration of visual acuity	Usually effective	Usually effective
Correction of visual field defects	Usually effective	Usually effective
Correction of diplopia	Not consistent; diplopia may develop after operation.	Not consistent; diplopia seldom changed after operation.
Usual hospitalization	5-6 days	10-12 days
Type of incision	Sublabial; no head shaving; no visible scar.	Bilateral frontal craniotomy; head shaved.
Mortality	0	0
Morbidity	Numb lip in all	None
Contraindications	Chronic sinusitis	None
Specific indication		When detailed exploration of orbits is advisable.

\*Reference 8 and 9

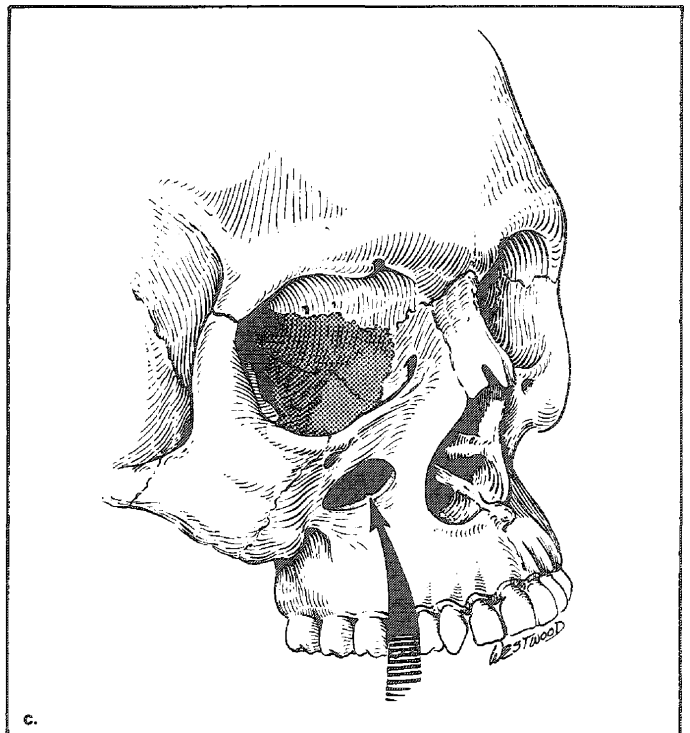
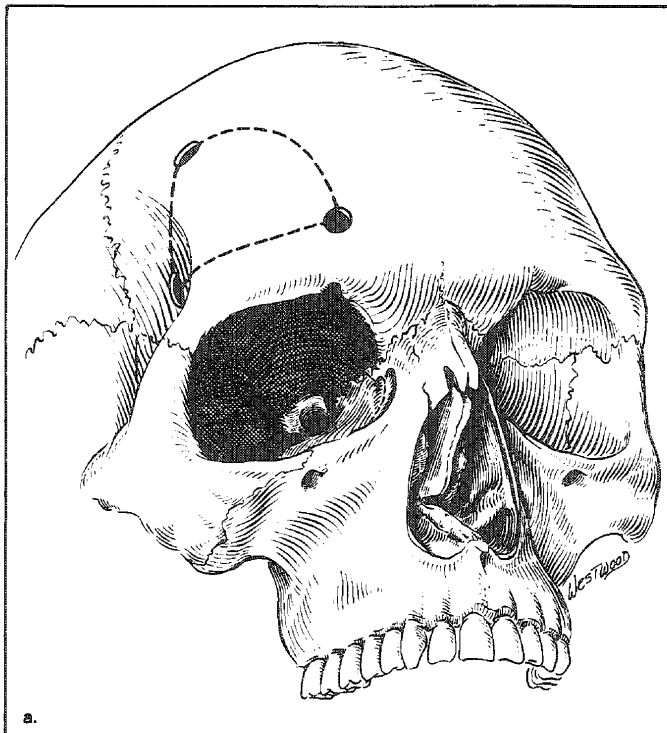
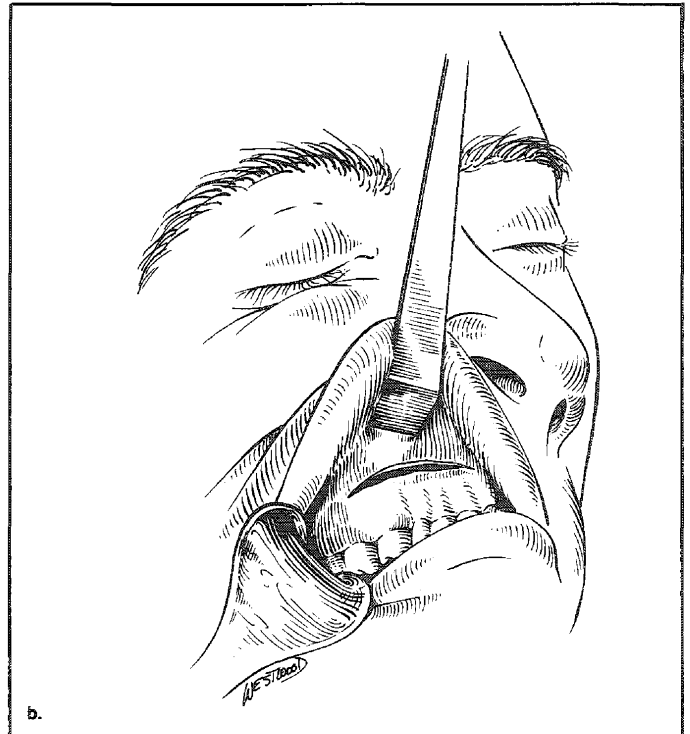
**Fig. 2—Margins of Transfrontal Craniotomy (Dotted Lines).**

a. The dark, shaded area represents orbital bone removed in this procedure.

**Transantral Decompression**

b. An incision is made inside the upper lid at the reflection of the gingival mucosa onto the cheek.

c. The floor and medial wall of the orbit (shaded area) are removed through the antrostomy.



Patients with Graves' disease, who have extraocular muscle function impairment typically first notice diplopia when looking upward and outward. Contrary to popular conception, this defect is caused not by weakness of the levators but by constraint from fibrosis and tightening of the inferior recti. This point can be demonstrated by the forced duction test, in which, using local anesthesia, the ophthalmologist inserts a muscle hook beneath the attachment of the inferior rectus and pulls in an attempt to elevate the globe. In cases where there is only paresis of the levators the globe will move upward easily. In Graves' disease the fibrosis of the inferior recti prevents the eye from moving upward. Recession of the inferior rectus attachment is the most commonly needed eye muscle procedure in patients with Graves' ophthalmopathy. If both orbital decompression and muscle surgery are planned, the decompression should always precede the muscle surgery, and muscle surgery should not be attempted in patients whose diplopia is still evolving, since a satisfactory correction may be undone by further progression of the condition.

As a result of the work of Callahan, Beard, and Quickert,<sup>7</sup> the anatomy of the eyelid is now understood in detail. Minor degrees of lid retraction can be easily corrected by section of Müller's muscle which is attached to the tarsal plate and the underside of the levator palpebrae superioris. By acting like a tightened bow string, it can elevate the upper lid. By cutting the "bowstring," the upper lid will lengthen and droop a few millimeters. More severe degrees of lid retraction can be corrected by insertion of a scleral graft in either the upper or lower lid.

### Summary

Management of patients with Graves' ophthalmopathy is a cooperative enterprise among an internist-endocrinologist, an ophthalmologist and an ENT surgeon or neurosurgeon. For the most severe cases rehabilitation may require diagnosis and correction of thyroid dysfunction, transantral orbital decompression followed by extraocular muscle surgery to correct diplopia, and scleral graft insertions in the upper and lower eyelids. For patients who are otherwise confronted with a serious threat to their vision or prolonged disfigurement, even this formidable series of procedures is welcome. Even patients with severe cosmetic disability or severe visual loss can be rehabilitated in most instances if skilled, coordinated, interdisciplinary care is provided and irreversible changes in optic nerve have not occurred. Lengthy delays in instituting treatment or a fatalistic attitude that nothing can be done are no longer justifiable.

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