Thyroid Eye Disease

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WILLIAMS & WILKINS
Baltimore • London • Los Angeles • Sydney

Editor: John N. Gardner
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Design: JoAnne Janowiak
Illustration Planning: Joseph P. Cummings
Production: Raymond E. Reter

Made in the United States of America

Library of Congress Cataloging in Publication Data

Char, Devron H., 1945-
Thyroid eye disease.

Includes bibliographies and index.
1. Thyroid eye disease. I. Title [DNLM: 1. Eye Manifestations. 2. Thyroid Diseases. WK 200 C469t] RC715.T48C43 1985 617.7 85-3342
ISBN 0-683-01519-2

Composed and printed at the
Waverly Press, Inc.

85 86 87 88 89
10 9 8 7 6 5 4 3 2 1

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To my parent Sylvia Char,
and my grandparents Samuel and
Mayme Char.

Preface

It is always difficult to review a large body of literature spanning almost two hundred years without inadvertently ignoring a contribution; hopefully this has been minimal. I have tried to limit the references principally to those in which there are primary data, papers which promulgated a major theory, or those which lucidly address the point footnoted. I am sure that some papers have not been cited which have made important inroads in our understanding, and I apologize in advance for those omissions.

In writing this book I very much appreciate the advice and assistance of my editor, Tara Mikesh, Barbara Tansill at Williams & Wilkins, Hanna Clark, Marly Ortega, and Elissa Murphy who have graciously produced word processed versions of this manuscript, and Mike Narahara for the photography. I am also in debt to Doctors Crowell Beard, Craig Hoyt, and Frank Greenspan who read portions of the manuscript and made valuable suggestions. Joan Widdell has, as usual, produced drawings which increase the lucidity of the text. Dr. David Norman and Robert D. Stone have kindly allowed me to use CT, MRI, and ultrasound data from our institution. They have all added much positive input; I take sole responsibility for the errors.

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CHAPTER 1

Introduction

The association between eye disease and hyperthyroidism has been recognized for almost 200 years. Parry (1) first described diffuse toxic goiter and proptosis in 1786. In 1835 Graves (2) described a female patient: "It was now observed that the eyes assumed a singular appearance, for the eyeballs were apparently enlarged, so that when she slept or tried to shut her eyes, the eyelids were incapable of closing. When the eyes were open, the white sclerotic could be seen, to a breadth of several lines around the cornea." Perhaps Brain (3) made the most telling statement about thyroid ophthalmopathy when he wrote: "there is an exception to every statement that can be made."

There have been more than 40 theories proposed to account for the development of eye changes in hyperthyroidism since von Basedow (4) hypothesized that the orbital contents were probably hypertrophied ("strumous hypertrophy"). The disproven hypotheses for thyroid ophthalmopathy include: cervical sympathetic stimulation, laxity of the extraocular muscles, orbital venous congestion, contraction of the nonstriated orbital muscles, and the presence of a simple pituitary factor (5–14).

There are many terms and classifications which have been advocated by various clinicians to describe thyroid eye findings (Table 1.1), including malignant exophthalmos, infiltrative ophthalmopathy, endocrine exophthalmos, and thyroid ophthalmopathy (15–19). Over 30 eponyms for various eye signs of thyroid ophthalmopathy exist (see Chapter 4).

This book is written for medical practitioners who manage patients with thyroid-related eye problems. The thyroid eye disease literature, even excluding those publications addressing Graves' disease in general, is voluminous. Approximately 800 manuscripts have been published on thyroid ophthalmopathy since its first clinical description in 1786. The etiology, pathophysiology, diagnosis, and treatment of hyperthyroidism and its associated ophthalmopathy remain an enigma to many physicians who must evaluate and treat patients with these condi-

Table 1.1.
Thyroid and Euthyroid Ophthalmopathy: Descriptive Terms

Thyrotoxic exophthalmos
Progressive exophthalmos
Malignant exophthalmos
Exophthalmic ophthalmoplegia
Thyrotropic exophthalmos
Hyperophthalmopathic form of Graves' disease
Edematous exophthalmos of endocrine origin
Infiltrative ophthalmopathy
Endocrine exophthalmos
Exophthalmic goiter
Thyrotropic exophthalmos
Postoperative exophthalmos
Exophthalmic ophthalmoplegia

tions. In some areas researchers and clinicians have improved our understanding of these disease processes; orbital scanning procedures have increased diagnostic accuracy and have demonstrated the mechanism of thyroid optic neuropathy (see Chapter 6). In other areas, historical theories, unsupported by controlled clinical trials, still influence the management of thyroid ophthalmopathy. As discussed in Chapter 6, the effect of various hyperthyroidism therapies (surgery, drugs, and radioactive iodine) on thyroid eye disease is still unclear.

A number of major issues remain unresolved in thyroid ophthalmopathy. These include:

1. What is the relationship between thyroid disease and eye findings? Are these components of the same disease or are they separate, but closely related, entities?
2. What is the role of the thyroid in the development of euthyroid ophthalmopathy?
3. Why do some patients with hyperthyroidism develop eye changes while other patients do not?
4. What is the relationship between the course of treated systemic thyroid disease and thyroid ophthalmopathy?
5. Why do a small minority of thyroid ophthalmopathy patients develop serious ocular sequelae while most do not?
6. What are the inciting factors for and pathogenesis of thyroid eye disease?
7. What mechanisms are responsible for asymmetric thyroid disease with either unilaterality or predominant inferior rectus muscle involvement?

This book stresses the diagnosis and management of thyroid eye disease and offers ophthalmologists a thorough overview of the associated eye changes. While there have been some excellent reviews of components of thyroid ophthalmopathy, no central text has brought these diverse areas together (20–30). The purpose of the present work is to consolidate current ideas of pathogenesis, diagnosis, and management. Chapter 2 is an overview of current concepts regarding thyroid regulation and the pathophysiology of Graves' disease. Chapter 3 discusses the use of nonocular tests in establishing the diagnosis of thyroid ophthalmopathy. Chapter 4 covers the eye signs, differential diagnoses, ocular tests, and orbital studies useful in diagnostic evaluation. Chapter 5 discusses current concepts of pathogenesis and pathophysiology. Chapter 6 outlines the natural history of thyroid eye disease; it includes the development of major complications such as restrictive myopathy, exposure, optic neuropathy, and the effect of systemic therapy on the ocular disease. The remainder of the book suggests a rational approach to the management of thyroid eye disease. An overview of treatment is presented and medical, radiation, and surgical approaches to therapy are outlined. A surgical atlas covers most of the procedures which this author has found useful in the management of thyroid ophthalmopathy.

References

1. Parry CH: Enlargement of thyroid gland in connection with enlargement or palpitation of the heart. Collections from unpublished medical writings of the late Caleb Hillier Parry. London, Underwoods, 1825, vol 2, p 111.
2. Graves RJ: Newly observed affection of the thyroid gland in females. *London Med Surg J* 7:516–520, 1835.
3. Brain R: Discussion of endocrine exophthalmos. *Proc R Soc Med* 45:237–244, 1952.
4. Von Basedow CA: Exophthalmos durch Hypertrophie des Cellgewebes in der Augenhohle. *Wochenschr Ges Heilk* 6:197 and 220, 1840.
5. Cooper WW: On protrusion of the eyes in connection with anemia, palpitation and goitre. *Lancet* 1:551–554, 1849.
6. Dobyns BM: Present concepts of pathologic physiology of exophthalmos. *J Clin Endocrinol Metab* 10:1202–1230, 1950.
7. Askanasy M: Pathologische-Anatomische Beitraege zur Kenntnis des Morbus Basedowii, insbesonders ueber die dabei auftretende Muskelerkrankung. *Dtsch Arch Klin Med* 61:118, 1898.
8. Sattler H: Ueber den sogenannten Landstroemischen Muskel und seine Bedeutung fuer den Exophthalmus bei Morbus Basedowii. *Ber Versamml Ophthalmol Ges Heidelberg* 37:181–187, 1911.
9. Mulvany JH: Exophthalmos of hyperthyroidism, part I. *Am J Ophthalmol* 27:589–611, 1944.

10. Aran FA: De la nature et du traitement de l'affection connue sous le nom de goitre exophthalmique, cachexia exophthalmique, maladie de basedow. *Bull Acad Med* 26:122, 1860–1861.
11. Marine D: Studies on pathological physiology of exophthalmos of Graves' disease. *Ann Intern Med* 12:443–453, 1938.
12. Bernard C: *Lecons sur la physiologie et la pathologie due systeme nerveux.* Paris, J. B. Balliere et Fils, 1858, vol 2, p 499.
13. Loeb J, Friedman H: Exophthalmos produced by injections of acid extract of anterior pituitary gland of cattle. *Proc Soc Exp Biol Med* 29:648–650, 1932.
14. Smelser GK: A comparative study of experimental and clinical exophthalmos. *Am J Ophthalmol* 20:1189–1203, 1937.
15. Brain WR: Exophthalmic ophthalmoplegia. *Tr Ophthalmol Soc UK* 57:107–115, 1937.
16. Jensen VA: Malignant exophthalmus after strumectomy. *Acta Ophthalmol* 18:1–20, 1940.
17. Thomas HM Jr, Woods AC: Progressive exophthalmos following thyroidectomy. *Bull Johns Hopkins Hosp* 59:9–113, 1936.
18. Warner F: Ophthalmoplegia externa, complicating a case of Graves' disease. *Br Med J* ii:843, 1882.
19. Werner SC: Ocular manifestations In Werner SC, Ingbar S (eds): *The Thyroid.* New York, Harper & Row, 1971, pp 528–550.
20. McGill DA, Asper SP Jr: Endocrine exophthalmos. A review and a report on autoantibody studies. *N Engl J Med* 267:188–193, 1962.
21. Woods AC: The ocular changes of primary diffuse toxic goitre; review. *Medicine* 25:113–153, 1946.
22. Havard CWH: Endocrine exophthalmos. *Br J Med* 1:1360–363, 1972.
23. Gorman CA: The presentation and management of endocrine ophthalmopathy. *Clin Endocrinol Metab* 7:67–96, 1978.
24. Kriss JP, Konishi J, Herman M: Studies on the pathogenesis of Graves' ophthalmopathy (with some related observations regarding therapy). *Recent Prog Horm Res* 31:533–566, 1975.
25. DeSanto LW: The total rehabilitation of Graves' ophthalmopathy. *Laryngoscope* 90:1652–1678, 1980.
26. Sergott RC, Glaser JS: Graves' ophthalmopathy. A clinical and immunologic review. *Surv Ophthalmol* 26:1–21, 1981.
27. Jacobson DH, Gorman CA: Endocrine ophthalmopathy: Current ideas concerning etiology, pathogenesis and treatment. *Endocr Rev* 5:200–220, 1984.
28. Kriss JP, McDougall IR, Donaldson SS: Graves' ophthalmopathy. In Krieger DT, Bordin CW (eds): *Therapy in Endocrinology.* Philadelphia, Decker, 1983.
29. Mullin BR: Dysthyroid exophthalmos. In Garner A, Klintworth GK (eds): *Pathobiology of Ocular Disease: A Dynamic Approach.* New York, Dekker, 1983, Pt B, p 1077.
30. Cordes FC: Endocrine exophthalmos: evaluation of present knowledge. *Am J Ophthalmol* 38:1–21, 1954.

CHAPTER 2

Normal Thyroid Gland and Mechanisms of Hyperthyroidism

NORMAL ANATOMY AND PHYSIOLOGY

The thyroid gland weighs approximately 20 grams; its upper isthmus margin can be palpated just below the cricoid cartilage. The gland has a rich vascular and lymphatic supply. Kriss and co-workers have demonstrated, using radionucleide tracer techniques, that the lymphatic drainage from both the thyroid gland and the orbit is into the cervical lymph node chain (1).

The thyroid gland is composed primarily of acini, or follicles, closely packed saccules invested with a rich capillary network. The clear proteinous colloid they contain constitutes the thyroid's major mass. Iodination and the initial phase of hormone secretion occur at or near the apical microvilli of follicular cells located in the colloid (2). Thyroglobulin, a protein which is the major component of the colloid, is the matrix in which thyroid hormones are formed and stored.

A hypothalamic-anterior pituitary-thyroid complex, modulated by a negative feedback loop, regulates thyroid function (Fig. 2.1) (3, 4). The cerebral cortex may also play a role, by regulating hypothalamic secretion of the TSH-releasing hormone TRH. TRH, a tripeptide synthesized in the supraoptic and paraventricular nuclei of the hypothalamus, is stored in the median eminence and reaches its target organ through the hypophyseal portal venous circulation. In the anterior pituitary it is specifically bound to thyrotroph and lactotroph cells and stimulates adenylate cyclase.

TRH acts to promote the release and synthesis of the thyroid stimulating hormone, thyrotropin (TSH), by bonding with thyrotroph cells in the anteromedial portion of the adenohypophysis. This action is inhibited mainly by unbound (free) T_4 and T_3 hormones, which diminish the number of available TRH receptors on pituitary thyrotrophs. Although TRH and thyroid hormones are the major components of the homeostatic control

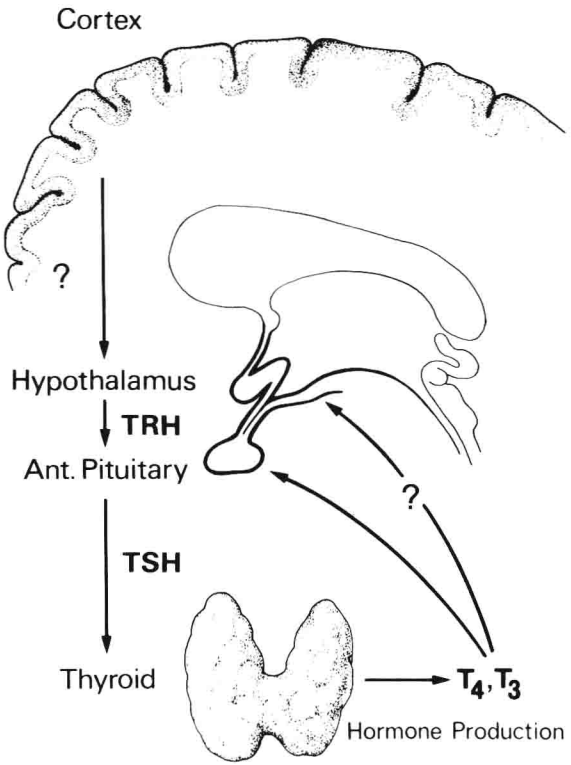

Figure 2.1. Schematic diagram of hypothalamic-anterior pituitary-thyroid interactions.

mechanism for TSH release, somatostatin, dopamine, steroids, iodide, and other compounds can all modulate this servocontrol circuit.

The glycoprotein TSH is composed of alpha and beta subunits (5). Many of its effects on the thyroid gland are mediated by cyclic AMP. In addition to the exogenous anterior pituitary influence, the thyroid gland also has some autoregulatory capacity.

Hormone formation in the thyroid gland occurs in three steps: active iodide transportation into the thyroid, iodide oxidation and iodination with tyrosyl residues to form inactive iodotyrosines, and coupling of iodotyrosines to form T_4 (thyroxine) and T_3. Release of hormones from the thyroid gland is also an active process requiring thyroglobulin hydrolysis and release of iodo-

thyronines (T_4 and T_3) prior to exit into the lymphatic and systemic circulations.

Almost all thyroid hormone is released as T_4 (thyroxine); peripheral conversion of that hormone produces more than 80% of the body's T_3 (6). T_4 is highly bound to two serum proteins, thyroxine binding alpha globulin (TBG) and thyroxine binding prealbumin (TBPA) (7). T_3 binds mainly to TBG. Both T_4 and T_3 are minimally bound to plasma albumin. Numerous conditions alter TBG concentrations (Table 2.1); while these do not affect the amount of hormone which enters the cell, they can artifactitiously alter the laboratory assessment of T_4 and T_3 levels. Some systemic illnesses, pregnancy, and drugs can also alter both hormone secretion and the peripheral conversion of T_4 to T_3.

MANIFESTATIONS OF HYPERTHYROIDISM

Hyperthyroidism (termed von Basedow's disease in Europe) most commonly presents in the third or fourth decade of life with a female:male ratio between 4:1 and 7:1 (8, 9). The United States incidence of this disease is estimated to be 0.4% (10). Thyrotoxicosis can result from overproduction of hormone by the thyroid (true hyperthyroidism), from inflammation-induced glandular hormone leakage, from oral ingestion of excess thyroid hormone, or (rarely) as a result of extrathyroidal hormone production.

Graves' disease or diffuse toxic goiter, actually a constellation

Table 2.1.
Thyroxine Binding Alpha Globulin (TBG) Alterations

1. Increases TBG levels
   a. Genetic predisposition
   b. Pregnancy
   c. Neonatal period
   d. Drugs: estrogens, birth control pills, perphenazine, etc.
   e. Liver disease: biliary cirrhosis, hepatitis
2. Decreases TBG levels
   a. Genetic predisposition
   b. Steroids
   c. Systemic illness
   d. Nephrotic syndrome
   e. Acromegaly

of disorders including diffuse primary thyroid hyperplasia and thyrotoxicosis, is one of a number of conditions associated with elevated levels of thyroid hormones. It is often accompanied by ophthalmopathy and occasionally by an infiltrative dermopathy. Rare hyperthyroid patients develop thyroid acropathy, which encompasses endocrine exophthalmos, pre-tibial myxedema and peripheral clubbing.

Other causes of thyrotoxicosis which are not associated with ophthalmopathy include toxic multinodular goiter, toxic adenoma, inappropriate thyroid stimulation (tumors, molar pregnancy, hypothalamic-pituitary abnormalities, etc.), thyrotoxicosis factita and diffuse micronodular goiter (11). Only in Graves' disease is there a statistically significant increased prevalence of eye disorders although eye findings occur in approximately 2% of Hashimoto's disease patients and occasionally in individuals with primary hypothyroidism, thyroid cancer, and those with a history of other forms of thyroid inflammation (12–15).

While eye signs and symptoms can be present at the time of diagnosis in 20–40% of Graves' disease patients, less than 20% of hyperthyroid patients initially present to their physician because of ocular manifestations without a history of hyperthyroidism (18–27). Most hyperthyroid patients seek medical care because of the systemic signs and symptoms of thyrotoxicosis: gradually occurring nervousness, irritability, emotional lability, fatigue, weight loss, abnormal heat sensitivity, increased sweating, palpitations, and weakness. In individual cases, different elements of this symptom complex may predominate. Occasionally patients seek help because of excess thyroid hormones, or after exacerbation of other systemic illnesses such as cardiac disease, or with acute thyrotoxicosis. The frequency of signs and symptoms in 247 thyrotoxic patients is shown in Table 2.2 (28).

In all forms of true hyperthyroidism there are increased levels of circulating T_3 and T_4; the serum T_3 is usually increased proportionately more than the T_4 concentration, leading to an abnormally elevated T_3/T_4 ratio. In as many as 10% of hyperthyroid patients, only T_3 levels are elevated (T_3 toxicosis). A significant number of patients referred to ophthalmologists for the diagnosis of proptosis have thyroid ophthalmopathy with normal or borderline elevated T_4 and elevated T_3 levels (16, 17). In almost all forms of hyperthyroidism, TSH secretion is sup-

Table 2.2.
Signs and Symptoms in Thyrotoxicosis Patients[a]

% of Cases	Symptoms	Signs
85–100	Nervousness, sweating, heat insensitivity, palpitation, fatigue, weight loss	Tachycardia, goiter, skin changes, tremor
70–85	Tachycardia, dyspnea, weakness	Thyroid bruit, eye signs
30–65	Increased appetite, eye symptoms, leg swelling, increased bowel movements	

[a] Modified from Williams, RH: Thiouracil treatment of thyrotoxicosis: the results of prolonged treatment. *J Clin Endocrinol* 6:1, 1946.

pressed, making thyrotropin levels either low or unmeasurable. In these situations the thyroid gland functions independently of the pituitary-hypophyseal axis.

An enlarged thyroid gland (goiter) and bilateral exophthalmos are the most characteristic signs of Graves' disease, present in approximately ⅓ of patients at the time of diagnosis (29–31). (Eye signs are discussed in detail in Chapter 4.) The thyroid gland is usually diffusely enlarged in hyperthyroid patients; however, many patients examined first because of eye findings have a normal gland, depending on the evolution of the thyroid gland pathology (22, 25). When there is diffuse enlargement of the gland, a thrill may often be palpable and a bruit audible over the thyroid. Patients usually have a tremor, warm, moist skin, and tachycardia, appear flushed due to increased cutaneous blood flow, and display nervous behavior. Often there are other integumentary changes including hair loss, brittleness, or increased fineness, soft nails, increased skin pigmentation, and vitiligo.

PATHOGENESIS OF HYPERTHYROIDISM

A number of clinical and research observations document the autoimmune nature of Graves' disease; however, neither the initiating events nor the precise immunopathology is well delineated (32–36). Graves' disease, Hashimoto's thyroiditis, and pri-