THE EPIDEMIOLOGIC CHARACTERISTICS AND CLINICAL COURSE OF OPHTHALMOPATHY ASSOCIATED WITH AUTOIMMUNE THYROID DISEASE IN OLMSTED COUNTY, MINNESOTA*

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INTRODUCTION

OPHTHALMIC ABNORMALITIES PUTATIVELY ASSOCIATED WITH THYROID dysfunction have long interested ophthalmologists and have been the subjects of several theses for the American Ophthalmological Society.[1-6] The goal of this study is to describe the epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in a population-based setting. Additionally, this work reviews the history of the recognition of thyroid ophthalmopathy and discusses the evolution of diagnostic and classification systems for the disease as related to the design and execution of the current epidemiologic study.

BACKGROUND

HISTORICAL PERSPECTIVES

The original description of thyroid ophthalmopathy is credited to Caleb Hillier Parry (1755-1822) (Fig 1). Parry was born in Cirencester, Gloucestershire, studied medicine in Edinburgh, and established a practice in Bath in 1779. In August 1786, Parry examined a 37-year-old woman who was the first of several patients with "enlargement of the thyroid gland in connection with enlargement or palpitation of the heart." Parry attributed the thyroid swelling to "bronchocele" and additionally noted that the patient's "eyes were protruded from their sockets, and the countenance exhibited an

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FIGURE 1
Caleb Hillier Parry. (Photograph of an engraving by Philip Audinet from a miniature sketch done by John Hay Bell in 1804.) (Courtesy of Mayo Foundation History of Medicine Library.)

appearance of agitation and distress, especially on any muscular exertion, which I have rarely seen equalled." Parry's description did not appear in print until 1825, when a collection of his unpublished medical writings became available in book form.[7] Although perhaps best known for his observations concerning the thyroid, Parry also published essays on English rhubarb, wild endives, the cause of decay in wood, and the breeding of racehorses and sheep.[8] Additionally, he was a childhood and lifelong friend of Edward Jenner, who dedicated his classic paper on cowpox vaccination to Parry. One of Parry's sons, Sir William Edward, achieved fame as an arctic explorer.[9]

Robert James Graves (1796-1853) (Fig 2) was born in Dublin, educated at Trinity College (Dublin), and studied in Göttingen, Berlin, Vienna, Copenhagen, and Edinburgh before returning to Dublin in 1821 to commence practice. During the 1834-1835 session of the Meath Hospital, Graves delivered a lecture in which he described three women who had palpitations and thyroid swelling.[10] The heart disorder was "violent and long continued. . .I could distinctly hear the heart beating when my ear was distant at least four feet from her chest!" Graves identified the thyroid as the cause of the palpitations and ascribed the gland's enlargement to "hypertrophy" rather than to goiter or bronchocele. A fourth patient, whom Graves did not examine but whose records were provided to him by a friend, was included in his report. The individual was a 20-year-old woman who had had signs and symptoms of thyrotoxicosis for at least 1 year, when "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 lids were incapable of closing. When the eyes were open, the white sclerotic could be seen, to a breadth of several lines, all round the cornea."

Taylor,[11] in his excellent biography of Graves, noted that it is unfortunate that Graves is best remembered for a disorder that he was neither the first person to describe nor in which he had a particular interest (there is no other reference to the disease in his published works), because he made several other notable contributions to medicine. For example, he described angioneurotic edema 30 years before Quincke and noted the phenomenon of idiopathic, paroxysmal, bilateral blanching and cyanosis of the digits from vascular constriction 20 years before Raynaud's description of the syndrome.[11] Graves' most important and lasting medical achievement, however, may be the initiation and popularization of clinical teaching at the patient's bedside.

Karl A. von Basedow (1799-1854) (Fig 3) was born in Dessau, Germany, studied medicine at Halle and in Paris, and established his practice in 1822 in the village of Merseburg.[12] In 1840, 5 years after the report by Graves,

FIGURE 2
Robert James Graves.

FIGURE 3
Karl A. von Basedow.

von Basedow[13] published the descriptions of four patients, all of whom had "a goitrous swelling of the thyroid" and "intumescence of the cellular tissue behind the bulbus."[14] In one patient, "there was a noticeable protrusion of

the eyeballs which were otherwise healthy and functioned completely, although she slept with open eyes. She had a frightened look and was known in our whole town as a crazy woman."[12] Two additional patients, both of whom were women, apparently had similar clinical courses. He wrote that "one could see the sclera above and below the cornea. The eyelids were spread wide apart and with much force was unable to bring them together, and she slept with wide open eyes. . . .One could not push the tense, bulging eyeballs back. She had to blink often and had a small stream of tears in order to keep the conjunctiva from shrinking, and because of inadequate cooling had eye infections. Her sight remained unaltered. . . ."[12] Additionally, one of the patients, who had pretibial myxedema, improved after ingestion of mineral water (which presumably contained iodides), one patient (a 50-year-old man) underwent bilateral enucleation for corneal ulcerations and perforations, and one patient's signs and symptoms improved during pregnancy. Although von Basedow's descriptions of eye involvement were superior to those of Parry and Graves, he attributed the constellation of thyroid and ophthalmic abnormalities to an unusual form of tuberculosis. The term "Merseburg triad" has been used as a synonym for the association of goiter, ophthalmopathy, and skin changes.

Werner[14] reviewed the early published reports on the disorder with hopes of clarifying proper nomenclature and concluded that "the situation is confused." Recognizing that the observations of Parry, Graves, and von Basedow each had strengths and weaknesses, he was "almost tempted to offer the eponym 'P-G-B disease' as a fairer tribute to all."

THE DIAGNOSIS OF GRAVES' OPHTHALMOPATHY

For many years, myriad terms such as dysthyroid ophthalmopathy, thyroid ophthalmopathy, thyroid orbitopathy, euthyroid ophthalmopathy, euthyroid Graves' disease, thyrotoxic exophthalmos or proptosis, exophthalmos of endocrine origin, infiltrative ophthalmopathy, malignant exophthalmos or proptosis, endocrine exophthalmos or proptosis, and thyroid eye disease have been used interchangeably (and often rather vaguely) to describe characteristic ophthalmic signs (including proptosis or exophthalmos, eyelid retraction, lid lag, restrictive extraocular myopathy, or optic neuropathy) that may accompany Graves' disease, hypothyroidism, or Hashimoto's thyroiditis. In some patients, typical eye findings occur in the absence of objective evidence of thyroid dysfunction ("euthyroid Graves' disease"), which many investigators attribute to inadequate sensitivity and specificity of available laboratory tests. Because the term "Graves' ophthalmopathy" (GO) probably is the most widely used description in the United States for this entity, for the purposes of this study it is used as a synonym for the

above designations.

Hamilton and colleagues[15] wrote in 1967 that "it is difficult to establish objectively what constitutes ophthalmopathy." The more recent comments of Rosen and Burde[16]—"currently, semantic confusion reigns"—and Feldon[17]—"the definition of Graves' ophthalmopathy is obscure"—suggest that precise diagnostic criteria remain elusive even though hundreds of scholarly reports have been published in the interim concerning the disease entity. The absence of a consensus definition for ophthalmopathy associated with autoimmune thyroid disease has resulted in a predictably wide spectrum of inclusion criteria in published studies. A review of comments from notable reports illustrates this variability and leads to the definition used in the current study.

McKenzie,[18] in 1968, defined Graves' disease as "a syndrome characterized by one or more of the following features, each one pathognomonic in itself: (1) diffuse hyperplasia (with or without nodularity) of the thyroid gland, usually with goiter and hyperthyroidism; (2) ophthalmopathy, which includes, variably, proptosis, ophthalmoplegia, and an inflammatory or 'infiltrative' affection of the orbit and periorbital tissues; (3) infiltrative dermopathy." This definition has been cited by more recent authorities as being the most workable and pragmatic.[16,19,20]

Hall and colleagues,[21] in 1970, described a group of 26 euthyroid patients without a history of thyroid disease: "The ocular features accepted to allow a clinical diagnosis of Graves' disease were: unilateral or bilateral lid retraction with no alternative explanation (eg, disease of the brain-stem); unilateral exophthalmos and lid retraction (unilateral or bilateral); bilateral exophthalmos; ophthalmoplegia affecting superolateral gaze associated with bilateral lid retraction or exophthalmos."

Solomon and associates,[22] in a widely cited paper published in 1977 on euthyroid Graves' disease, indicated that GO was diagnosed simply by "clinical features," ie, "All had Graves's ophthalmopathy, classes 2 through 5 in the American Thyroid Association classification."

Gorman,[23] in 1978, noted that most patients with GO pose little diagnostic difficulty when the characteristic ocular manifestations exist concomitantly with clinical and laboratory evidence of hyperthyroidism. However, "When the history of hyperthyroidism is absent and the plethora of manifestations. . .[pain, lacrimation, photophobia, blurring of vision, double vision] is reduced to a few, and when they affect only one eye, the diagnosis may become very difficult and it then often rests on the unconstitutional premise of 'guilt by association'. In other words, the clinician who encounters eye findings that are compatible with, but not diagnostic of, Graves' ophthalmopathy seeks evidence of another type that thyroid function or its

regulation is disordered, and if such evidence is forthcoming, he then presumes to link it to the diagnostically nonspecific eye findings to conclude that they are due to endocrine exophthalmos."

Waller and Jacobson[24] presented in 1984 a diagnostic "pie diagram" (Fig 4) that was conceived by Gorman[25] but not published under his name until 1986. These authors noted that eyelid retraction is a frequent clinical feature of GO and emphasized its preeminence as a diagnostic criterion. The "pie" was divided into four quadrants according to secondary diagnostic findings: extraocular muscle involvement, optic neuropathy, proptosis, and thyroid dysfunction. In their opinion, when eyelid retraction is present in concert with all four of the secondary diagnostic criteria, "the diagnosis is assured. When all of the features in one quadrant are present, the diagnosis is considered likely. Isolated involvement of the eyelids, muscles, or nerves leaves the diagnosis open to question."[24]

A similar approach was advocated by Hay,[26] who wrote in 1984 that "The concurrence of bilateral lid retraction with proptosis and ophthalmoplegia is quite diagnostic, whereas the isolated occurrence of periorbital edema, chemosis, conjunctival injection, proptosis, or extraocular muscle dysfunction in one eye is nonspecific. Although no single finding is pathognomonic, certain patterns can be considered diagnostic. When all the major clinical and laboratory features of Graves' disease are present, the diagnosis is ensured."

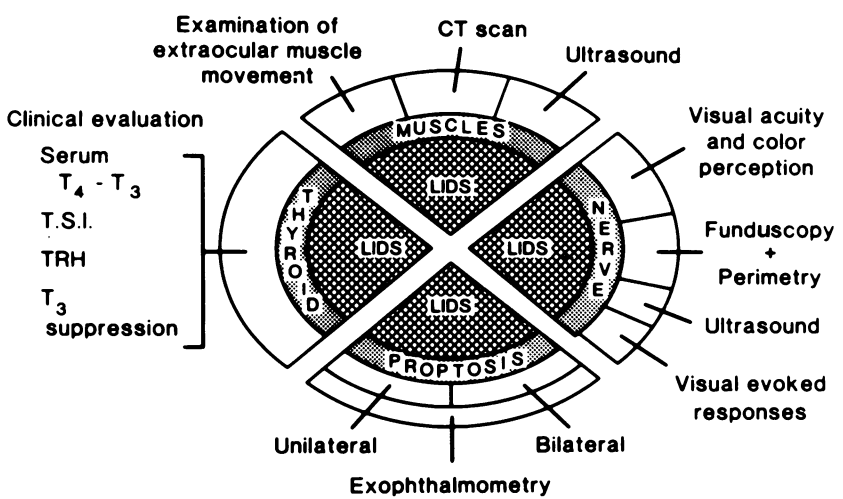

FIGURE 4

Clinical and laboratory findings associated with endocrine ophthalmopathy. CT, computed tomography; TRH, thyrotropin-releasing hormone; TSI, thyroid-stimulating immunoglobulin. (From Waller and Jacobson.[24] By permission of Mayo Foundation.)

Leone[27] reported in 1984 a series of 124 patients with ophthalmic Graves' disease. No specific diagnostic criteria were given; rather, the author indicated that patients were referred by an internist or endocrinologist after a diagnosis of hyperthyroidism had been made "or because of proptosis, diplopia, or asymmetry in eyelid configuration. . . .Occasionally, patients would present initially with vague complaints of tearing, hyperemia of the conjunctiva, or fullness in the periorbital area." Some patients had computed tomographic evidence of enlarged extraocular muscles, whereas "in very early cases, the only signs were lid lag and mild periorbital edema."

Perhaps the most precise published definition of GO was proposed by Frueh[5] in 1984 in his thesis for the American Ophthalmological Society: "For the purpose of this study, Graves' eye disease has been defined as the presence of one of the following three sets of characteristics:

(1) A history of a thyroid disorder; the presence of at least two of the following: exophthalmos, lid retraction, and extraocular muscle involvement; and bilaterality shown by CT scan or noted for any of the three preceding clinical findings.

(2) The presence of exophthalmos, lid retraction, and extraocular muscle involvement, at least two of which must be bilateral.

(3) A positive CT scan and at least two of the following on at least one side: exophthalmos, lid retraction, and extraocular muscle involvement."

In Frueh's study,[5] a computed tomography scan was considered positive if there were at least two enlarged extraocular muscles in one orbit and at least one enlarged extraocular muscle in the other orbit, exophthalmos was defined as an exophthalmometer reading of ≥ 20 mm, eyelid retraction was considered to be present if the lid fissure was > 11 mm or if the upper eyelid margin was ≥ 7 mm from the center of the pupil, and extraocular muscle involvement was defined as restriction of at least one muscle.

Burde and coworkers,[28] in 1985, concluded "that the most critical sign to look for is the presence of lid retraction. We believe this lid sign is so specific it can be used as a primary indicator of thyroid-related proptosis [cited Hall and associates[21]]. . . .If lid retraction is present, the diagnosis of dysthyroid orbitopathy is established."[29]

The fundamental diagnostic importance of eyelid retraction was reiterated by Bahn and coworkers[30] in 1988: "Eyelid retraction is the most consistent clinical feature of GO; in its absence, the diagnosis cannot be made with complete confidence."

Wiersinga and colleagues,[31] in an article published in 1988, diagnosed GO "according to the following criteria[32]: (1) clinical presentation of eye disease consistent with Graves' ophthalmopathy; (2) extraocular muscle enlargement and/or increased retroorbital fat mass on orbital CT-scan. . .;

and (3) exclusion of an alternative diagnosis in doubtful cases by additional investigations."

Sridama and DeGroot,[33] in a study published in the *American Journal of Medicine* in 1989, relied on exophthalmos as an important clinical feature of GO; the diagnosis required proptosis of ≥ 20 mm, or 18 to 20 mm if other obvious signs of infiltrative ophthalmopathy (inflamed extraocular muscles, diplopia, chemosis) were present or if extraocular muscle enlargement was evident by computed tomography.

Feldon,[34] in 1990, expressed a different view: "Exophthalmos is the most commonly measured and perhaps the most overrated sign of Graves' ophthalmopathy." In his opinion, "Few signs are as characteristic of Graves' ophthalmopathy as are lid retraction and lid lag."

Three studies published in 1993 by experienced teams of ophthalmologists and internists demonstrate that precise inclusion or exclusion criteria are not the rule. In a report by Prummel and Wiersinga[35] from Amsterdam, GO was diagnosed from "characteristic eye signs and symptoms in the presence of enlarged extraocular eye muscles on a coronal computed tomographic scan of the orbits and past or present Graves' hyperthyroidism." Kendler and associates[36] published a detailed survey of initial clinical findings in 557 consecutive patients with GO who were referred to the Thyroid Orbitopathy Clinic at the University of British Columbia. In their study, "The diagnosis of thyroid orbitopathy was clinical, supported by the results of thyroid function tests and computed tomography of the orbit, in most cases." Similar criteria were used by Perros and colleagues[37] from the United Kingdom: "The diagnosis of TAO [thyroid associated ophthalmopathy] was made on the basis of clinical features, and when in doubt by orbital computed tomography (by demonstrating enlargement of the extraocular muscles)."

Two decades ago, Franco and coworkers[38] recognized the difficulty that faces investigators who study and treat patients with GO: "A simple reliable test to confirm the clinical diagnosis of euthyroid Graves' disease would be helpful to avoid unnecessary diagnostic procedures and therapy." The above examples illustrate that the diagnosis, at present, remains clinical. Although the criteria proposed by Gorman[25] and Frueh[5] are the most specific, exceptions may occur. For example, a patient could have objective evidence of thyroid dysfunction, infiltrative ophthalmopathy with optic neuropathy, and bilateral extraocular muscle involvement that is confirmed by computed tomography. If exophthalmos and lid retraction were absent, which might be the case in a "tight" orbit, the patient would not satisfy either Gorman's or Frueh's diagnostic criteria of GO. Gorman's "pie" includes eyelid retraction in each "slice," and Frueh's criteria require two of three ophthalmic

features (exophthalmos, lid retraction, or extraocular muscle involvement) plus thyroid dysfunction to fulfill set 1, bilaterality of at least two of the three ophthalmic features in the absence of thyroid dysfunction to fulfill set 2, or a positive computed tomographic scan plus at least two of the three ophthalmic features to fulfill set 3.

Until a laboratory test or other determinant that is specific for GO is available, the following alternative diagnostic criteria are proposed (Table I). GO is considered to be present if eyelid retraction (upper eyelid position at or above the superior corneoscleral limbus) occurs together with objective evidence of thyroid dysfunction (preferably including, but not limited to, serum thyroid-stimulating immunoglobulins[39-41]) or exophthalmos (defined as a Krahn or Hertel exophthalmometry measurement ≥ 20 mm, which, although arbitrary, probably is reasonable in the Olmsted County population, in which whites of western European ancestry predominate), or optic nerve dysfunction, or extraocular muscle involvement (either restrictive myopathy or enlarged muscles as determined by computed tomography, magnetic resonance imaging, or ultrasonography). The ophthalmic signs may be either unilateral or bilateral, and confounding causes (such as idiopathic orbital inflammation ["pseudotumor"], lymphoma, sarcoidosis, amyloidosis, vasculitis, contiguous sinus disease, cellulitis, orbital tumors or

TABLE I: DIAGNOSTIC CRITERIA FOR GRAVES' OPHTHALMOPATHY*

Eyelid retraction†	plus	Thyroid dysfunction‡ or Exophthalmos§ or Optic nerve dysfunction// or Extraocular muscle involvement¶
	OR (in the absence of eyelid retraction)	
Thyroid dysfunction‡	plus	Exophthalmos§ or Optic nerve dysfunction// or Extraocular muscle involvement¶

*The ophthalmic signs may be either unilateral or bilateral, and confounding causes must be excluded.
†Upper eyelid position at or above the superior corneoscleral limbus.
‡Objective evidence.
§Krahn or Hertel measurement ≥20 mm.
//Abnormal visual acuity, pupillary reaction, perimetry, or color vision not attributable to other causes.
¶Restrictive myopathy or objective evidence of enlarged muscles.

vascular malformations, posterior commissure brain lesions, medication-induced proptosis [eg, lithium or corticosteroids], or hydrocephalus) must be excluded. If eyelid retraction is absent, then GO may be diagnosed only if exophthalmos, or optic nerve involvement, or restrictive extraocular myopathy coexist(s) with thyroid dysfunction and no other cause(s) for the ophthalmic feature(s) is (are) apparent. This definition has been accepted by the endocrinologists and ophthalmologists at our institution who collaborate in the care of patients with GO and was used as the inclusion criteria for the current study.

CLASSIFICATION OF GRAVES' OPHTHALMOPATHY

"One of the most difficult and controversial areas that has preoccupied workers in this field is the classification of severity. . . .It is clear that an ideal system for grading TAO [thyroid-associated ophthalmopathy] does not exist. . . ."[37]

The most well-known and widely used classification system for GO is the NOSPECS outline, which was introduced by the American Thyroid Association in 1969.[42] Subsequently, numerous classification schemes have been proposed, the more notable of which include the ophthalmopathy index proposed by Donaldson and colleagues in 1973,[43] the American Thyroid Association's modified NOSPECS in 1977,[44,45] Van Dyk's RELIEF variation of NOSPECS in 1981,[46] Feldon's system based on seven clinical signs,[47] Kahaly and associates' 1986 activity score derived from anamnestic data,[48] Bahn and Gorman's 1987 recommendation of eliminating soft tissue signs and relying solely on objective criteria,[49] Mourits and colleagues' classification in 1989 based on dolor, rubor, tumor, and functio laesa,[50] and finally the 1992 consensus of the major international thyroid societies to abandon NOSPECS for clinical studies in lieu of reporting only measurable data.[51] A detailed review of the evolution of classification schemes is included in Appendix 1[52-82]; for the purposes of this study, however, the consensus recommendations were followed.

SUBJECTS AND METHODS

STUDY SETTING

Epidemiologic studies in Rochester, Minnesota, and Olmsted County, Minnesota, are possible because the city and county are relatively isolated from other urban centers and because the population is served by a largely unified medical care system that has accumulated comprehensive clinical records over many years. Rochester, Minnesota (1990 population: 69,995),

lies 90 miles southeast of Minneapolis and St. Paul. Approximately 70% of the county population resides within the city limits of Rochester, the centrally located county seat. Demographic information about Rochester and Olmsted County is available from each published decennial census. In 1990 the population was 96% white, and 28% of the population was older than 45 years. The population is largely middle class, and approximately 82% of adults have graduated from high school. With the exception of a higher proportion of the working population employed in the health care industry, the characteristics of the population of Rochester and Olmsted County are similar to those of United States whites. The results of many previous population-based studies from Rochester and Olmsted County have demonstrated that the data from the proposed report should be applicable at least to the white population of the United States. Extrapolating findings from this study to groups not represented within the county, however, could be problematic.

Most medical care for citizens of Rochester and Olmsted County is provided by the Mayo Clinic, a tertiary referral center with more than 1,000 full-time staff physicians representing most medical and surgical specialties and subspecialties. Two major hospitals, Saint Marys and Rochester Methodist, with a combined total of 1,400 beds, are affiliated with the Mayo Clinic. Although serving as a major referral institution, the Mayo Clinic also provides comprehensive primary and secondary care for the region, including Olmsted County. Prior to 35 years ago, medical service was available through the Mayo Clinic, the Rochester State (psychiatric) Hospital, and a few independent practitioners. Since then, the Olmsted Medical Group and its associated Olmsted Community Hospital have provided an additional independent source of multispecialty medical care. The ophthalmologists at the Olmsted Medical Group, however, routinely refer patients with symptomatic autoimmune thyroid ophthalmopathy to the Mayo Clinic. Additionally, all persons diagnosed with hyperthyroidism at the Olmsted Medical Group who require thyroid ablation either with radioactive iodine or operation are referred to our institution.

The epidemiologic potential of this situation is enhanced by each provider using a unit (or dossier) medical record system whereby all data collected on an individual are assembled in one place.[83] The Mayo Clinic unit record, for example, contains the details of every inpatient hospitalization at its two large affiliated hospitals; every outpatient visit to the office or clinic, the emergency rooms, nursing homes, or private homes; laboratory and pathologic results (including autopsies); and correspondence concerning the patient. The unit records of each provider in the county have been maintained and are readily available for use. The Mayo Clinic medical files currently

contain more than 4,400,000 medical histories (including referral patients); fewer than 500 records have been lost in more than 80 years. Each year, more than 60% of the Rochester population is seen at one of the Mayo Clinic facilities, and nearly 100% is seen within a 3-year period. The medical details are collected by physicians for subspecialty-level medical care and in general are of high quality. Of relevance to the current project, endocrinologists and ophthalmologists at the Mayo Clinic have developed a large referral practice for the care of patients with thyroid disorders and associated eye abnormalities. (For example, 733 patients with Graves' disease were examined at the Mayo Clinic in 1990; 311 patients were noted to have ophthalmopathy, and in 154 patients the eye changes were diagnosed for the first time.) To enhance patient care and to help accumulate information for clinical research, approximately 20 years ago endocrinologists at the Mayo Clinic began to record information on patients with GO in a fairly standardized manner by use of a form that is included in the medical record (Appendix 2); ophthalmologists have used a printed stamp with similar categories.

The medical records are easily retrievable because the Mayo Clinic has maintained, since the early 1900s, extensive indices based on clinical and histologic diagnoses and surgical procedures. The Rochester Epidemiology Project (RO1 AR-30582) has developed a similar index for the records of all other providers of medical care to Rochester and Olmsted County residents. In addition to the Mayo Clinic, these are the Olmsted Medical Group, the Olmsted Community Hospital, the University of Minnesota Hospital and Veteran's Administration Hospital in Minneapolis, all of the small hospitals in the surrounding counties, and the few independent medical practitioners in Rochester. The result is linkage of medical records from essentially all sources of medical care available to and utilized by the Rochester and Olmsted County population. Death certificates also are indexed for Rochester and Olmsted County residents. This centralized system now encompasses the medical records of a population with an estimated 2,500,000 person-years of experiences. The potential of this data resource for population-based studies has been described elsewhere.[84]

In addition to describing the incidence and prevalence of disease entities, this unique environment provides an ideal setting in which to assess practice patterns and service utilization in a population-based setting. Furthermore, because of the ability to follow patients longitudinally through their medical records, this setting allows for an assessment of the long-term effects of these practice patterns. The following paragraphs describe the methods with which this epidemiologic laboratory was used to assess the occurrence and subsequent clinical course of ophthalmopathy associated with autoimmune thyroid disease.

CASE IDENTIFICATION

A retrospective, population-based incidence and prevalence cohort of Olmsted County residents who came to medical attention for ophthalmopathy associated with autoimmune thyroid disease between Jan 1, 1976, and Dec 31, 1990, inclusive, was identified. Potential cases were identified through the medical diagnostic index, drawn from persons included under the diagnostic rubrics of Graves' ophthalmopathy, dysthyroid ophthalmopathy, thyroid ophthalmopathy, thyroid orbitopathy, euthyroid ophthalmopathy, thyrotoxic exophthalmos/proptosis, exophthalmos of endocrine origin, infiltrative ophthalmopathy, malignant exophthalmos/proptosis, endocrine exophthalmos/proptosis, Graves' disease, thyrotoxicosis, hyperthyroidism, euthyroid Graves' disease, autoimmune thyroid disease with thyrotoxicosis, Hashimoto's thyroiditis with ophthalmopathy, thyroid eye disease, hypothyroidism with ophthalmopathy, or myxedema with ophthalmopathy.

Once identified, all records coded under the diagnoses of GO, Graves' disease, or their synonyms were reviewed (n = 1,102). Ophthalmic examinations had been recorded in 814 (73.9%) of these charts. Because it was anticipated that very few additional patients with ophthalmopathy would be identified under the headings of hypothyroidism and Hashimoto's thyroiditis (n = 4,204) who had not been coded as having ophthalmopathy at some point in their medical course, a 10% systematic sample was drawn from a chronologic list of these records. No new patients with ophthalmopathy were found among the 420 individuals, of whom 307 (73.1%) had an ophthalmic examination recorded.

All 1,522 records were reviewed by the author; additionally, to help enhance the accuracy of data collection, the charts of patients with more complicated medical courses were independently abstracted by an endocrinologist who is experienced in the care of patients with GO, or by an ophthalmologist-in-training, or both. Most of the records, therefore, were reviewed by two individuals, and many charts were abstracted by three physicians.

During a complete review of the medical history, pertinent demographic, clinical, and laboratory data were transcribed onto a precoded paper abstracting form. Demographic information included date of birth, sex, race, residence at date of diagnosis of GO, and residence 1 year before date of diagnosis of GO. Regarding ophthalmopathy, the dates of first sign, first symptom, diagnosis, diagnosis at the Mayo Clinic, and initial ophthalmic examination were noted. Data were recorded at the first and at subsequent ophthalmic examinations for the following symptoms, signs, or factors: diplopia, blurred vision, pain or ocular discomfort, lacrimation, photophobia, visual acuity (Snellen), visual field, color vision, eyelid retraction,

lagophthalmos, eyelid lag, eyelid fullness, exophthalmometry, corneal staining, superior limbic keratoconjunctivitis, conjunctival injection, chemosis, extraocular muscle dysfunction, resistance of the globe to retropulsion, intraocular pressure, optic disk appearance, and the presence of choroidal folds. If diplopia was present, it was categorized into one of the following groups: present only when fatigued, present in extremes of gaze, constant but correctable by prisms, or constant and not correctable by prisms. Eyelid retraction and lagophthalmos were graded as mild (< 2 mm), moderate (2 to 4 mm), or severe (> 4 mm). Eyelid fullness was rated as mild, moderate, or severe but was not quantitated.

Information on the patient's medical status included determination of thyroid status (hyperthyroidism, primary hypothyroidism, Hashimoto's thyroiditis, or euthyroidism). The date of dysthyroid symptoms, if present, and the characteristics found on thyroid palpation were noted. Data regarding the following characteristics and variables were recorded: treatment for thyroid dysfunction, development of posttreatment hypothyroidism, history of head or neck irradiation, history of tobacco use, presence of systemic disorders, pregnancy or occurrence of a major stressful life event (such as divorce, death of a family member, motor vehicle accident, loss of job) within 6 months of diagnosis of thyroid dysfunction, presence of thyroid dermopathy or acropachy, and family history of thyroid disease. Laboratory tests related to thyroid function, including total thyroxine, free thyroxine, triiodothyronine, thyroid-stimulating hormone, sensitive thyroid-stimulating hormone, thyroid-stimulating immunoglobulin, microsomal antibody titer, thyroglobulin antibody titer, ^{131}I uptake, thyrotropin-releasing hormone stimulation, and fine-needle thyroid aspiration, were recorded for the times of initial diagnosis of thyroid dysfunction and ophthalmopathy and at subsequent examinations. The normal values at our institution for these laboratory tests are outlined in Appendix 3.

Treatments for GO were recorded, including the use of systemic corticosteroids, orbital radiotherapy, or surgical procedures. If corticosteroids other than prednisone were used, the dose was multiplied by an appropriate factor to translate into "prednisone equivalents."

The dates of last clinical data and of last follow-up were obtained from the record. If the patient was deceased, the date and cause of death were noted. The patient's last-known status in terms of diplopia, ocular discomfort, visual acuity, and thyroid function was recorded.

Once collected, the abstracted data were entered into a computer and verified by trained data entry personnel. The data were edited with various online range and consistency checks by a biostatistical data analyst.

Incident cases were persons who were residents of Olmsted County,

Minnesota, on the index date of diagnosis of GO by a physician. Residence was verified using information from birth certificates, city and county directories, or earlier medical records. Each subject's residency status was determined on the index date and 1 year before the index date to identify anyone from the cohort who may have moved to Olmsted County specifically to facilitate the diagnosis and treatment of conditions associated with ophthalmopathy.

Detailed age-specific and sex-specific population figures for 1976 through 1990 were derived by a linear interpolation of age-specific and sex-specific decennial census figures for 1970 through 1990. With these denominators, age-specific and sex-specific incidence rates for ophthalmopathy associated with autoimmune thyroid disease were calculated both overall and for 5-year periods from 1976 through 1990. Summary rates were adjusted to the (5-year) age distribution of US whites in 1990 using the direct method. Interval estimates were calculated about the point estimates assuming a Poisson error distribution. Secular trends were modeled using Poisson regression.[85] Persons identified for the incidence cohort were followed through their medical records at all providers of care to ascertain the clinical course of ophthalmopathy associated with autoimmune thyroid disease in terms of treatments, resolution and recurrence of signs and symptoms, and subsequent morbid events.

All persons not known to be deceased were sent a mail questionnaire that elicited information about ocular symptoms, subsequent evaluation and treatment of ophthalmopathy performed outside Olmsted County since the examination at our institution, and the patient's and family's past medical history to supplement data abstracted from the medical record. This follow-up vehicle also was used to update the vital status of study subjects.

Patients who did not return the questionnaire were followed up using a strategy similar to that designed for The Second Natural History Study of Congenital Heart Defects.[86] All follow-up was conducted through the Survey Research Center at the Mayo Clinic. Briefly, the standard procedures for follow-up start with a review of the patient's medical record. The records are reviewed for the patient's last-known address and telephone number and last-known treating physician's address and telephone number. Telephone directories or directory assistance is used to check the current address and telephone number for the patient (or next of kin). If this process does not yield a confirmed current address for the patient or relative, the last-known treating physician is contacted. For patients not located by these basic steps, further sources are used to obtain more recent information: the patient's employers, the patient's college, departments of public health and vital statistics, driver's license bureaus, city directories,

and TRW Financial Services.

The cumulative probabilities of the need for radioiodine therapy and surgical intervention were estimated according to the method of Kaplan and Meier.[87] Differences between strata based on prognostic factors were tested using the log-rank test. The association between potential prognostic factors and outcomes was assessed in several ways. When outcomes were measured as a time to outcome (with censoring at last-known follow-up), Cox proportional hazards models were derived to estimate the association of these outcomes with continuous risk factors and with combinations of risk factors. Tests of the assumption of proportional hazards were performed as suggested by Harrell and Lee.[88]

RESULTS

DEMOGRAPHICS, INCIDENCE RATES, INCLUSION CRITERIA, AND CHRONOLOGY

During the 15-year interval from 1976 through 1990, 120 incident cases of GO were diagnosed among residents of Olmsted County, Minnesota (Table II). The number of patients per year who were diagnosed with the disorder ranged from 4 in 1976 and 1984 to 12 in 1979 and 1982.

General demographic data are outlined in Table III. Seventeen (14.2%) of the patients were male and 103 (85.8%) were female ($P = .00001$; normal relative deviate test). All patients were white. At the time of diagnosis of GO, 82 (68.3%) of the patients lived within the city limits of Rochester, whereas 38 patients (31.7%) resided elsewhere in Olmsted County. This distribution is similar to the population density recorded in the most recent census, which showed that 66% of Olmsted County inhabitants resided in Rochester.[89] One year before the diagnosis of GO, 81 persons (67.5%) were residents of Rochester, 35 (29.2%) lived elsewhere in Olmsted County, and 4 (3.3%) resided outside the county. None of these four patients moved to Olmsted County primarily to facilitate medical care at the Mayo Clinic or the Olmsted Medical Group.

The incidence rates of GO are outlined in Tables IV through VI and Fig 5. The overall age-adjusted incidence rate for females was 16.0 cases/100,000 population/year, whereas the rate for males was 2.9 cases/100,000 population/year (standardized rate ratio = 5.5; 95% confidence interval [CI], 3.3 to 9.3). The distribution of incidence rates by 5-year age groups is outlined in Table IV; of note is the peak incidence rates in the age groups 40 to 44 years and 60 to 64 years in females and 45 to 49 years and 65 to 69 years in males.

Incidence rates for the city of Rochester, Minnesota, and for the remainder of Olmsted County are detailed in Tables V and VI, respectively. The

TABLE II: FREQUENCY DISTRIBUTION OF INCIDENT CASES OF GRAVES' OPHTHALMOPATHY

YEAR OF DIAGNOSIS	NO. OF CASES	%
1976	4	3.3
1977	8	6.7
1978	11	9.2
1979	12	10.0
1980	6	5.0
1981	11	9.2
1982	12	10.0
1983	7	5.8
1984	4	3.3
1985	8	6.7
1986	4	3.3
1987	9	7.5
1988	9	7.5
1989	7	5.8
1990	8	6.7
	120	100.0

TABLE III: DEMOGRAPHIC DATA FOR 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY

CATEGORY	NO. OF CASES	%
Sex		
Male	17	14.2
Female	103	85.8
Race		
White	120	100
Residence at diagnosis of ophthalmopathy		
Rochester, Minnesota	82	68.3
Remainder of Olmsted County, Minnesota	38	31.7
Residence 1 year before diagnosis of ophthalmopathy		
Rochester, Minnesota	81	67.5
Remainder of Olmsted County, Minnesota	35	29.2
Other than Olmsted County, Minnesota	4	3.3

TABLE IV: INCIDENCE RATES FOR OPHTHALMOPATHY, 1976 THROUGH 1990, IN ALL OF OLMSTED COUNTY, MINNESOTA

	FEMALE		MALE	
AGE (YR)	NO.	INCIDENCE RATE/ 100,000/YEAR	NO.	INCIDENCE RATE/ 100,000/YEAR
5-9	2	3.4737	0	0.0000
10-14	1	1.7952	1	1.6919
15-19	2	3.3322	0	0.0000
20-24	7	10.3082	1	1.9083
25-29	11	15.3820	3	4.5319
30-34	13	19.5207	1	1.5931
35-39	7	12.9116	1	1.8989
40-44	15	32.8299	1	2.2866
45-49	7	18.8192	5	13.4160
50-54	8	24.5602	1	3.1596
55-59	8	27.8658	0	0.0000
60-64	9	35.8723	1	4.5188
65-59	3	13.1729	2	11.0552
70-74	3	14.6987	0	0.0000
75-79	2	11.5788	0	0.0000
80+	5	19.0687	0	0.0000
Total	103		17	
Age-adjusted rate			95% confidence interval	
Females	16.0252		12.8889-19.1615	
Males	2.9117		1.4889-4.3345	

TABLE V: INCIDENCE RATES FOR OPHTHALMOPATHY, 1976 THROUGH 1990, IN ROCHESTER, MINNESOTA

AGE (YR)	FEMALE NO.	FEMALE INCIDENCE RATE/ 100,000/YEAR	MALE NO.	MALE INCIDENCE RATE/ 100,000/YEAR
5-9	2	5.9775	0	0.0000
10-14	1	3.1627	1	3.0031
15-19	1	2.7054	0	0.0000
20-24	6	11.6451	1	2.8432
25-29	8	15.8381	1	2.1706
30-34	11	24.7024	1	2.3988
35-39	5	14.8681	1	3.1070
40-44	6	21.4217	0	0.0000
45-49	5	22.1288	2	9.2976
50-54	7	33.8704	1	5.3277
55-59	6	31.8201	0	0.0000
60-64	6	34.8331	1	7.1505
65-69	1	6.1828	1	8.9501
70-74	3	19.6425	0	0.0000
75-79	1	7.4085	0	0.0000
80+	3	14.0004	0	0.0000
Total	72		10	
Age-adjusted rate			95% confidence interval	
Females	16.5463		12.6543-20.4382	
Males	2.7693		0.9934-4.5051	

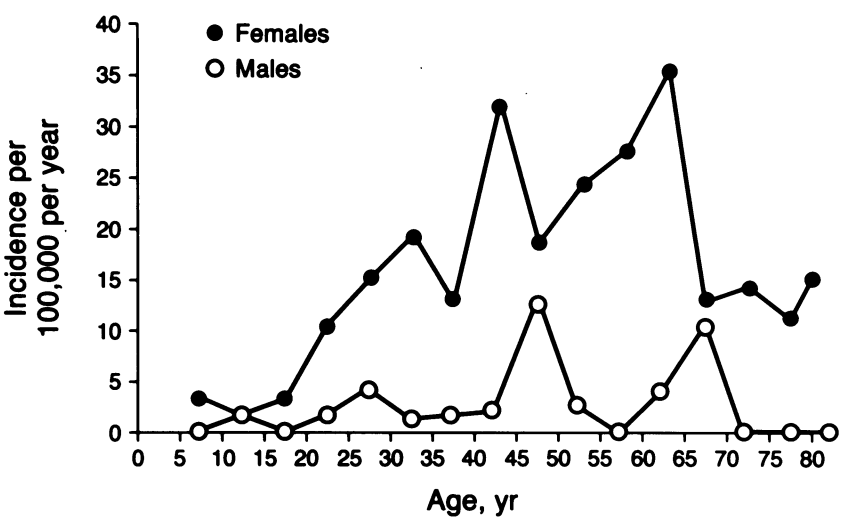

FIGURE 5
Incidence rates of Graves' ophthalmopathy in Olmsted County, Minnesota, 1976 through 1990.

TABLE VI: INCIDENCE RATES FOR OPHTHALMOPATHY, 1976 THROUGH 1990, REMAINDER OF OLMSTED COUNTY, MINNESOTA

	FEMALE		MALE	
AGE (YR)	NO.	INCIDENCE RATE/ 100,000/YEAR	NO.	INCIDENCE RATE/ 100,000/YEAR
5-9	0	0.0000	0	0.0000
10-14	0	0.0000	0	0.0000
15-19	1	4.3369	0	0.0000
20-24	1	6.1039	0	0.0000
25-29	3	14.2850	2	9.9369
30-34	2	9.0637	0	0.0000
35-39	2	9.7153	0	0.0000
40-44	9	50.9021	1	5.5590
45-49	2	13.6977	3	19.0379
50-54	1	8.3991	0	0.0000
55-59	2	20.2984	0	0.0000
60-64	3	38.1485	0	0.0000
65-69	2	30.3030	1	14.4550
70-74	0	0.0000	0	0.0000
75-79	1	26.4901	0	0.0000
80+	2	41.7275	0	0.0000
Total	31		7	
Age-adjusted rate			95% confidence interval	
Females	15.5217		9.9036-21.1398	
Males	3.1993		0.7753-5.6233	

difference in age- and sex-adjusted incidence rates for Rochester, Minnesota, compared with the remainder of Olmsted County was not statistically significant (P = .98; normal relative deviate test).

Age-adjusted incidence rates by 5-year intervals (1976 through 1980, 1981 through 1985, and 1986 through 1990) are illustrated in Fig 6. The trends between intervals were not statistically significant.

The frequencies of features that were used for inclusion criteria are listed in Table VII. Unilateral right or left upper eyelid retraction was noted in 10 patients (8.4%) each, whereas bilateral upper eyelid retraction was present in 88 patients (73.9%). Information about lid retraction was not available for one patient. Therefore, 108 (90.8%) of the 119 incident cases had eyelid retraction at some point of the clinical course. Proptosis (an exophthalmometry measurement of 20 mm or more) was documented in 73 (62.4%) of the 117 patients for whom data were recorded. Exophthalmos affected the right eye alone in 2 patients (1.7%), the left eye only in 8 (6.8%), and both eyes in 63 (53.8%). Optic nerve function was compromised in the right eye only of 2 patients (1.7%), in the left eye only of 1 (0.8%), and in both

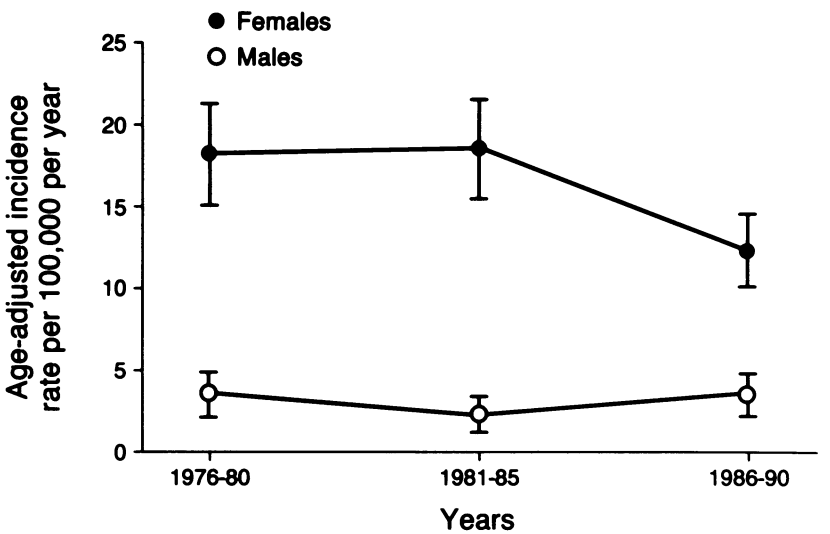

FIGURE 6
Age-adjusted incidence rates of Graves' ophthalmopathy in Olmsted County, Minnesota, 1976 through 1990, by 5-year intervals. Bars represent 1 SD.

eyes in 4 (3.3%). Seven patients (5.8%), therefore, had optic nerve dysfunction attributable to GO. Restrictive extraocular myopathy was noted for the right eye only in 5 patients (4.2%), for the left eye only in 8 (6.7%), and for both eyes in 38 (31.7%); unilateral or bilateral limitation of ocular ductions was documented in 51 patients (42.5%). Imaging studies (computed tomography, magnetic resonance imaging, ultrasonography, or more than one technique) to document extraocular muscle enlargement were performed in only 22 patients, as it has been the usual practice at our institution to perform such tests only when the diagnosis is uncertain or if orbital decompression is being considered, rather than as a routine part of the diagnostic evaluation. The muscles were enlarged in the right orbit only in 1 patient (4.5%), in the left orbit only in 2 (9.1%), and bilaterally in 9 (40.9%). Unilateral or bilateral extraocular muscle enlargement thus was confirmed in 12 (54.5%) of the 22 patients in whom imaging studies were performed. Thyroid dysfunction was confirmed by abnormal results of laboratory tests in 113 patients (94.2%) but was evident by some clinical measure at some point in the record in 111 patients (92.5%).

The classification of thyroid dysfunction was determined for each patient and is outlined in Table VIII. One hundred eight patients (90%) had classic Graves' hyperthyroidism, 1 patient (0.8%) had primary hypothyroidism, 4

TABLE VII: FREQUENCY OF FEATURES USED FOR INCLUSION CRITERIA AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY

FEATURE	NO.	%
Eyelid retraction (data for 119 patients)		
Right eye only	10	8.4
Left eye only	10	8.4
Both eyes	88	73.9
Exophthalmos (data for 117 patients)		
Right eye only	2	1.7
Left eye only	8	6.8
Both eyes	63	53.8
Optic nerve dysfunction		
Right eye only	2	1.7
Left eye only	1	0.8
Both eyes	4	3.3
Restrictive extraocular myopathy		
Right eye only	5	4.2
Left eye only	8	6.7
Both eyes	38	31.7
Evidence of extraocular muscle enlargement (data for 22 patients)		
Right eye only	1	4.5
Left eye only	2	9.1
Both eyes	9	40.9
Laboratory evidence of thyroid dysfunction	113	94.2
Clinical evidence of thyroid dysfunction	111	92.5

TABLE VIII: CLASSIFICATION OF THYROID DYSFUNCTION AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY

CATEGORY	NO.	%
Hyperthyroidism	108	90.0
Hypothyroidism	1	0.8
Hashimoto's thyroiditis	4	3.3
Euthyroidism	7	5.8

patients (3.3%) had Hashimoto's thyroiditis, and 7 patients (5.8%) were euthyroid throughout their medical course.

The frequencies of features used for inclusion criteria, in relation to the thyroid status, are recorded in Table IX. The three most common combinations of findings, affecting approximately two-thirds of patients, were hyperthyroidism, eyelid retraction, and exophthalmos (30 patients; 25%), hyperthyroidism plus eyelid retraction (26 patients; 21.7%), and hyperthyroidism, eyelid retraction, exophthalmos, and extraocular muscle involvement (25 patients; 20.8%). Six patients (5%) had the complete constellation of findings: eyelid retraction, exophthalmos, optic nerve dysfunction, extraocular muscle involvement, and hyperthyroidism. All of the patients with primary hypothyroidism, Hashimoto's thyroiditis, or euthyroidism had eyelid retraction, but none of these patients had optic nerve dysfunction.

The chronology among incident cases of GO is outlined in Table X. The average age at the time of diagnosis of thyroid dysfunction (excluding the seven patients with euthyroidism) was 42.2 ± 17.1 years (median, 41; range, 8.2 to 87.2), whereas the average age at the time of diagnosis of GO was 44.7 ± 17.4 years (median, 43.4; range, 8.2 to 88.7). Hyperthyroidism was diagnosed at a slightly later age in the 95 patients (88%) who had symptoms related to thyroid dysfunction than in the 13 patients (12%) who were asymptomatic (mean ages, 42.5 years versus 38.3 years, respectively; median ages, 40.8 years versus 37.2 years, respectively; $P = .4129$; two-sample t test). Similarly, ophthalmopathy was diagnosed more than 10 years later in the 69 patients with hyperthyroidism (63.9%) who had eye symptoms (blurred vision, diplopia, lacrimation, pain or ocular discomfort, or photophobia; mean age, 48.1 years; median age, 47.4 years) than in the 39 patients (36.1%) who had clinical signs but no ocular symptoms (mean age, 36.9 years; median age, 34.0 years); this difference was significant ($P = .0013$; two-sample t test). The onset of ophthalmopathy among the patients who had either Hashimoto's thyroiditis or euthyroid Graves' disease occurred later yet (mean ages, 52.8 and 52.6 years, respectively; median ages, 50.4 and 49.2 years, respectively), but the difference compared with the mean age at diagnosis of ophthalmopathy in the patients with hyperthyroidism (44.1 years) was not significant ($P = .297$, one-way analysis of variance). The average age at diagnosis of thyroid dysfunction was greater, but not significantly so, in the 4 patients with Hashimoto's thyroiditis (53.5 years) than in the 108 patients with hyperthyroidism (42.0 years; $P = .186$, two-sample t test).

GO was diagnosed at the same time as hyperthyroidism in 22 (20.3%) of the 108 patients with this subgroup of thyroid dysfunction. Ophthalmopathy was diagnosed in the 6-month interval before the diagnosis of hyperthyroid-

TABLE IX: FREQUENCY OF FEATURES USED FOR INCLUSION CRITERIA IN RELATION TO THYROID STATUS AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY

	FEATURES						
THYROID STATUS	EYELID RETRACTION	EXOPH-THALMOS	OPTIC NERVE DYSFUNCTION	EXTRAOCULAR MUSCLE INVOLVEMENT	THYROID DYSFUNCTION	NO.	%
Hyperthyroidism	x	x			x	30	25.0
	x				x	26	21.7
	x	x		x	x	25	20.8
	x			x	x	10	8.3
	x	x	x	x	x	6	5.0
				x	x	5	4.2
		x			x	3	2.5
		x		x	x	2	1.7
		x	x	x	x	1	0.8
Hypothyroidism	x				x	1	0.8
Hashimoto's thyroiditis	x				x	3	2.5
	x	x		x	x	1	0.8
Euthyroidism	x	x		x		3	2.5
	x	x				2	1.7
	x				x°	2	1.7

°Goiter.

TABLE X: CHRONOLOGY AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY

CATEGORY	AGE (YR)
All patients	
At diagnosis of thyroid dysfunction (113 patients)	
Mean	42.2 ± 17.1
Median	41
Range	8.2-87.2
At diagnosis of ophthalmopathy (120 patients)	
Mean	44.7 ± 17.4
Median	43.4
Range	8.2-88.7
Hyperthyroidism (108 patients)	
At diagnosis of thyroid dysfunction	
Mean	42.0 ± 17.2
Median	40.1
Range	8.2-87.2
At diagnosis of ophthalmopathy	
Mean	44.1 ± 17.7
Median	42.8
Range	8.2-88.7
With hyperthyroid symptoms (95 patients; 88%)	
At first symptom	
Mean	41.2 ± 15.5
Median	39.5
Range	14.4-87
At diagnosis of hyperthyroidism	
Mean	42.5 ± 17.1
Median	40.8
Range	9.1-87.2
Without hyperthyroid symptoms (13 patients; 12%)	
At diagnosis of hyperthyroidism	
Mean	38.3 ± 18.4
Median	37.2
Range	8.2-81.8
With eye symptoms (69 patients; 63.9%)	
At first symptom	
Mean	47.6 ± 17.9
Median	46.9
Range	7.6-88.4
At diagnosis of ophthalmopathy	
Mean	48.1 ± 18.0
Median	47.4
Range	8.2-88.7
Without eye symptoms (39 patients; 36.1%)	
At diagnosis of ophthalmopathy	
Mean	36.9 ± 14.8
Median	34
Range	9.1-82.1
Hypothyroidism (1 patient)	
At diagnosis of hypothyroidism	27.1
At diagnosis of ophthalmopathy	27.1

TABLE X: CHRONOLOGY AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY (CONT'D)

CATEGORY	AGE (YR)
Hashimoto's thyroiditis (4 patients)	
At diagnosis of Hashimoto's thyroiditis	
Mean	53.5 ± 9.8
Median	50.8
Range	45.6-66.7
At diagnosis of ophthalmopathy	
Mean	52.8 ± 8.9
Median	50.4
Range	45.6-64.9
Euthyroidism (7 patients)	
At diagnosis of ophthalmopathy	
Mean	52.6 ± 15.3
Median	49.2
Range	32.5-76.2

ism in 20 patients (18.5%) and in the 6-month interval after thyroid diagnosis in 24 patients (22.2%). The diagnosis of GO was confirmed before the diagnosis of hyperthyroidism in only 4 additional patients (3.7%), whereas ophthalmopathy developed after hyperthyroidism in the remaining 38 patients (35.2%) in the cohort. These data are discussed later in this work in relation to a previous study (Fig 17).

The months of diagnoses of thyroid dysfunction and of GO were analyzed with the Rayleigh test[90] to determine whether a seasonal pattern was present. The monthly distribution of number of diagnoses is outlined in Table XI. There was no significant seasonal variation for either the diagnosis of thyroid dysfunction ($P > .10$) or the diagnosis of ophthalmopathy ($P > .10$).

GENERAL MEDICAL STATUS

Information regarding the medical history and clinical findings among the 120 incident cases is summarized in Table XII. These data were compiled both from review of the medical records and from information provided by patients in the follow-up questionnaire.

A family history of thyroid disease was documented in most (66 patients; 60.6%) of the 109 patients in whom such information was elicited. Hyperthyroidism was the most common type of dysfunction, and treatment more frequently involved complete or subtotal thyroid resection than radioactive iodine, as expected in an earlier medical era.

None of the patients in the incidence cohort were known to have undergone irradiation to the head or neck before the onset of thyroid disease.

TABLE XI: MONTH OF DIAGNOSIS OF THYROID DYSFUNCTION AND GRAVES' OPHTHALMOPATHY IN 120 INCIDENT CASES*

MONTH	DIAGNOSIS OF THYROID DYSFUNCTION*		DIAGNOSIS OF GRAVES' OPHTHALMOPATHY	
	NO.	%	NO.	%
January	5	4	8	7
February	9	8	8	7
March	18	16	16	13
April	9	8	8	7
May	8	7	11	9
June	4	4	7	6
July	14	12	13	11
August	7	6	8	7
September	6	5	11	9
October	10	9	13	11
November	13	12	10	8
December	10	9	7	6

*The seven patients with euthyroidism are not included.

TABLE XII: PERTINENT MEDICAL HISTORY AND FINDINGS AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY

CATEGORY	NO.	%
Family history of thyroid disease (data for 109 patients)	66	60.6
Hyperthyroidism	24	22.0
Hypothyroidism	22	20.1
Both	6	5.5
Goiter	22	20.1
Thyroid cancer	0	0
Surgery required for thyroid disease	22	20.1
Radioiodine therapy required for thyroid disease	11	10.1
History of head or neck irradiation before onset of thyroid disease (data for 111 patients)	0	0
History of tobacco use (data for 111 patients)		
Ever smoked cigarettes	60	54.1
No. of years		
Mean, 21.9 ± 13.7		
Median, 20		
Range, 2-61		
Currently smoking cigarettes	38	34.2
No. per day		
Mean, 10.4 ± 11.8		
Median, 8		
Range, 1-46		

TABLE XII: PERTINENT MEDICAL HISTORY AND FINDINGS AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY (CONT'D)

CATEGORY	NO.	%
Pregnancy (data for 90 females)	65	72.2
Onset of thyroid disease		
During pregnancy	4	6.2
≤6 mo after pregnancy	4	6.2
>6 mo after pregnancy	11	16.9
Onset of ophthalmopathy		
During pregnancy	3	4.6
≤6 mo after pregnancy	2	3.1
>6 mo after pregnancy	4	6.2
Major stressful life event within 6 mo of GO diagnosis (data for 111 patients)	5	4.5
Status of thyroid gland at diagnosis of thyroid dysfunction (data for 117 patients)		
Diffuse goiter	100	85.5
Nodular goiter	8	6.8
Thyroid normal to palpation	9	7.7
Thyroid dermopathy (pretibial myxedema) (data for 119 patients)	5	4.2
Thyroid acropachy (data for 119 patients)	1	0.8
Concomitant systemic disorders		
Type I (insulin-dependent) diabetes mellitus	0	0
Type II (non-insulin-dependent) diabetes mellitus	2	1.7
Myasthenia gravis	1	0.8
Rheumatoid arthritis	1	0.8
Systemic lupus erythematosus	0	0
Pernicious anemia	0	0
Ulcerative colitis	1	0.8
Crohn's disease	1	0.8
Rendu-Osler-Weber syndrome (hereditary hemorrhagic telangiectasia)	1	0.8
Paget's disease	1	0.8
Pituitary adenoma	1	0.8
Breast carcinoma	3	2.5
Laryngeal carcinoma	1	0.8
Fallopian tube carcinoma	1	0.8
Colon carcinoma	1	0.8

Approximately one half (54.1%) of patients with GO had smoked cigarettes, and 38 of 111 patients (34.2%) were current smokers. The number of cigarettes smoked per day is detailed in Table XII.

Nearly three of four females had been pregnant at least once, although it was difficult to determine accurately how many of these women were of childbearing age. However, during pregnancy, thyroid disease developed in four patients and ophthalmopathy developed in three patients; additionally, the onset of thyroid disease occurred within 6 months after delivery in four patients and ophthalmopathy developed in two patients during this same interval.

A major stressful life event, such as death of a family member, divorce, major financial difficulties, or an automobile accident, was documented in 5 (4.5%) of the 111 patients for whom information was available.

At the time of diagnosis of thyroid dysfunction, 100 patients (85.5%) had a diffuse goiter, 8 (6.8%) had a nodular goiter, and the thyroid gland was normal to palpation in 9 (7.7%). Information on the size and consistency of the gland was not available for three patients.

Thyroid dermopathy, also known as pretibial myxedema, was present in five patients (4.2%), and thyroid acropachy was diagnosed in one patient (0.8%); information on these two findings was unavailable for one patient.

Evidence of concomitant systemic disease, particularly autoimmune disorders, was sought. Three patients (2.5%) had breast carcinoma, two patients (1.7%) had type II (noninsulin-dependent) diabetes mellitus, and one person each (0.8%) had myasthenia gravis, rheumatoid arthritis, ulcerative colitis, Crohn's disease, Rendu-Osler-Weber syndrome, Paget's disease, pituitary adenoma, laryngeal carcinoma, fallopian tube carcinoma, and colon carcinoma. No persons had type I (insulin-dependent) diabetes mellitus, pernicious anemia, or systemic lupus erythematosus.

LABORATORY TESTS

The results of pertinent laboratory tests performed at the time of diagnosis of thyroid dysfunction, at the time of diagnosis of ophthalmopathy, and at the most recent examination are outlined in Table XIII for all 120 incident cases and in Table XIV for the 108 patients with hyperthyroidism; our institution's normal values for these tests are provided in Appendix 3.

Among all incident cases, the average total thyroxine value was 18.6 μg/dl when thyroid dysfunction was diagnosed and 14.6 μg/dl at the diagnosis of GO. Mean values for free thyroxine and triiodothyronine were similarly increased in most patients in whom they were determined. The thyrotropin-releasing hormone stimulation test and the thyroid-stimulating hormone (TSH) test were used for the diagnosis of thyroid dysfunction in the earlier

TABLE XIII: LABORATORY TEST RESULTS AT DIAGNOSIS OF THYROID DYSFUNCTION AND OF OPHTHALMOPATHY AND AT FINAL EXAMINATION AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY

TEST	AT DIAGNOSIS		AT FINAL EXAMINATION	DIFFERENCE BETWEEN VALUE AT DIAGNOSIS AND FINAL EXAMINATION	
	OF THYROID DYSFUNCTION	OF GO		THYROID DIAGNOSIS	GO DIAGNOSIS
Total thyroxine					
Mean (μg/dl)	18.6 ± 6.4	14.6 ± 7.9	8.6 ± 2.9	Mean, 10.2 ± 6.1;	Mean, 6.1 ± 7.6;
Median (μg/dl)	16.8	12.9	8.6	95% CI, 8.6-11.7	95% CI, 4.2-8.0
Range (μg/dl)	4.8-35.0	0.4-35.0	0.3-17.2	Median, 9.2; 95% CI,	Median, 4.8; 95% CI,
Normal, no. pt (%)	12 (12)	45 (42)	60 (84)	7.1-10.9	2.0-8.2
Increased, no. pt (%)	87 (87)	54 (51)	4 (6)	P = .0001 (signed-rank	P = .0001 (signed-rank
Decreased, no. pt (%)	1 (1)	7 (7)	7 (10)	test)	test)
	(data for 100 pt)	(data for 106 pt)	(data for 71 pt)	(data for 63 pt)	(data for 64 pt)
Free thyroxine					
Mean (ng/dl)	5.1 ± 2.3	3.7 ± 2.4			
Median (ng/dl)	4.6	3.0			
Range (ng/dl)	2.1-10.8	0.9-10.8			
Increased, no. pt (%)	34 (100)	33 (100)			
	(data for 34 pt)	(data for 33 pt)			
Triiodothyronine					
Mean (ng/dl)	414 ± 222	338 ± 253			
Median (ng/dl)	383	268			
Range (ng/dl)	6-984	14-984			
Normal, no. pt (%)	5 (15)	11 (35)			
Increased, no. pt (%)	28 (82)	19 (59)			
Decreased, no. pt (%)	1 (3)	2 (6)			
	(data for 34 pt)	(data for 32 pt)			
Thyrotropin-releasing hormone stimulation					
Normal, no. pt (%)	3 (75)	4 (66.7)			
Flat, no. pt (%)	1 (25)	2 (33.3)			
	(data for 4 pt)	(data for 6 pt)			

TABLE XIII: LABORATORY TEST RESULTS AT DIAGNOSIS OF THYROID DYSFUNCTION AND OF OPHTHALMOPATHY AND AT FINAL EXAMINATION AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY (CONT'D)

TEST	AT DIAGNOSIS		AT FINAL EXAMINATION	DIFFERENCE BETWEEN VALUE AT DIAGNOSIS AND FINAL EXAMINATION	
	OF THYROID DYSFUNCTION	OF GO		THYROID DIAGNOSIS	GO DIAGNOSIS
Thyroid-stimulating hormone					
Mean (μU/ml)	0.62 ± 1.1	13.5 ± 48.4	15.4 ± 28.5	Inadequate sample for comparison	Inadequate sample for comparison
Median (μU/ml)	0.3	0.9	3.4		
Range (μU/ml)	Undetectable to 3.9	Undetectable to 250	Undetectable to 98.3		
Normal, no. pt (%)	4 (27)	11 (41)	9 (53)		
Increased	0	4 (15)	6 (35)		
Decreased	11 (73)	12 (44)	2 (12)		
	(data for 15 pt)	(data for 27 pt)	(data for 17 pt)		
Sensitive thyroid-stimulating hormone					
Mean (mIU/l)	0.51 ± 2.0	5.7 ± 15.2	4.6 ± 9.6	Mean, −6.9 ± 14.3; 95% CI, −14.5-0.7	Mean, −0.7 ± 24.4; 95% CI, −14.2-12.8
Median (mIU/l)	0.05	0.05	1.2		
Range (mIU/l)	0-9.5	0-56.8	0-55.6	Median, −1.6; 95% CI, −4.9-0.3	Median, −0.5; 95% CI, −3.8-0
Normal, no. pt (%)	1 (5)	2 (10)	26 (55)		
Increased, no. pt (%)	1 (4)	4 (19)	9 (19)	$P \leq .01$ (signed-rank test)	$P > .10$ (signed-rank test)
Decreased, no. pt (%)	21 (91)	15 (71)	12 (26)		
	(data for 23 pt)	(data for 21 pt)	(data for 47 pt)	(data for 16 pt)	(data for 15 pt)
^{131}I uptake (at 24 hr)					
Mean (%)	63 ± 17	58 ± 22			
Median (%)	65	61			
Range (%)	15-92	8-92			
Normal, no. pt (%)	3 (4)	9 (15)			
Increased, no. pt (%)	82 (96)	51 (85)			
	(data for 85 pt)	(data for 60 pt)			

TABLE XIII: LABORATORY TEST RESULTS AT DIAGNOSIS OF THYROID DYSFUNCTION AND OF OPHTHALMOPATHY AND AT FINAL EXAMINATION AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY (CONT'D)

TEST	AT DIAGNOSIS		AT FINAL EXAMINATION	DIFFERENCE BETWEEN VALUE AT DIAGNOSIS AND FINAL EXAMINATION	
	OF THYROID DYSFUNCTION	OF GO		THYROID DIAGNOSIS	GO DIAGNOSIS
Thyroid-stimulating immunoglobulins (TSI)					
Mean (TSI index)	6.5 ± 4.5	7.6 ± 6.6			
Median (TSI index)	6.0	6.5			
Range (TSI index)	1-12	0-20			
Normal, no. pt (%)	2 (22)	3 (21)			
Increased, no. pt (%)	7 (78)	11 (79)			
	(data for 9 pt)	(data for 14 pt)			
Microsomal antibody titer					
Median	1:1,600	1:6,400			
Range	1:100-1:25,600	1:100-1:25,600			
Increased, no. pt (%)	11 (100)	13 (100)			
	(data for 11 pt)	(data for 13 pt)			
Thyroglobulin antibody titer					
Median	1:100	1:50			
Range	Undetectable to 1:100	Undetectable to 1:400			
Normal, no. pt (%)	4 (40)	5 (50)			
Increased, no. pt (%)	6 (60)	5 (50)			
	(data for 10 pt)	(data for 10 pt)			
Fine-needle aspiration biopsy of thyroid					
Abnormal	3 pt	(no data)			
	(data for 3 pt)				

CI, confidence interval; GO, Graves' ophthalmopathy.

TABLE XIV: LABORATORY TEST RESULTS AT DIAGNOSIS OF THYROID DYSFUNCTION AND OF OPHTHALMOPATHY AND AT FINAL EXAMINATION AMONG 108 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY WITH HYPERTHYROIDISM

TEST	AT DIAGNOSIS OF		AT FINAL EXAMINATION	DIFFERENCE BETWEEN VALUE AT DIAGNOSIS AND FINAL EXAMINATION	
	THYROID DYSFUNCTION	GO		THYROID DIAGNOSIS	GO DIAGNOSIS
Total thyroxine					
Mean (μg/dl)	19.0 ± 6.2	15.5 ± 7.8	8.7 ± 2.9	Mean, 10.6 ± 5.8;	Mean, 6.7 ± 7.5;
Median (μg/dl)	17.1	13.5	8.7	95% CI, 9.1-12.1	95% CI, 4.7-8.6
Range (μg/dl)	7.6-35	0.5-35	0.3-17.2	Median, 9.6; 95% CI,	Median, 5.3; 95% CI,
Normal, no. pt (%)	11 (11)	50 (52)	57 (88)	8.0-11.7	3.1-9.1
Increased, no. pt (%)	86 (89)	41 (43)	3 (4)	P =.0001 (signed-rank	P =.0001 (signed-rank
Decreased, no. pt (%)	0	5 (5)	5 (8)	test)	test)
	(data for 97 patients)	(data for 96 patients)	(data for 65 patients)	(data for 60 patients)	(data for 59 patients)
Free thyroxine					
Mean (ng/dl)	5.2 ± 2.3	4.1 ± 2.4			
Median (ng/dl)	4.7	3.8			
Range (ng/dl)	2.1-10.8	1-10.8			
Normal, no. pt (%)	0	3 (11)			
Increased, no. pt (%)	33 (100)	24 (89)			
	(data for 33 patients)	(data for 27 patients)			
Triiodothyronine					
Mean (ng/dl)	423 ± 218	383 ± 250			
Median (ng/dl)	384	382			
Range (ng/dl)	6-984	51-984			
Normal, no. pt (%)	5 (15)	9 (33)			
Increased, no. pt (%)	28 (85)	18 (67)			
	(data for 33 patients)	(data for 27 patients)			
Thyrotropin-releasing hormone stimulation	No data	No data			

TABLE XIV: LABORATORY TEST RESULTS AT DIAGNOSIS OF THYROID DYSFUNCTION AND OF OPHTHALMOPATHY AND AT FINAL EXAMINATION AMONG 108 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY WITH HYPERTHYROIDISM (CONT'D)

TEST	AT DIAGNOSIS OF		AT FINAL EXAMINATION	DIFFERENCE BETWEEN VALUE AT DIAGNOSIS AND FINAL EXAMINATION	
	THYROID DYSFUNCTION	GO		THYROID DIAGNOSIS	GO DIAGNOSIS
Thyroid-stimulating hormone					
Mean (μU/ml)	0.62 ± 1.1	3.9 ± 11.1	16.9 ± 30.1	Inadequate sample for comparison	Inadequate sample for comparison
Median (μU/ml)	0.3	0.3	3.4		
Range (μU/ml)	Undetectable to 3.9	Undetectable to 48	Undetectable to 93.3		
Normal, no. pt (%)	12 (80)	12 (55)	6 (40)		
Increased, no. pt (%)	0	2 (9)	5 (33)		
Decreased, no. pt (%)	3 (20)	8 (36)	4 (27)		
	(data for 15 patients)	(data for 22 patients)	(data for 15 patients)		
Sensitive thyroid-stimulating hormone					
Mean (mIU/l)	0.1 ± 0.3	5.8 ± 15.6	4.7 ± 9.9	Mean, −7.3 ± 14.7; 95% CI, −15.5-0.8	Mean, −0.7 ± 24.4; 95% CI, −14.2-12.8
Median (mIU/l)	0.05	0.05	0.98		
Range (mIU/l)	0-1.3	0-56.8	0-55.6	Median, −2.0; 95%	Median, −0.7; 95%
Normal, no. pt (%)	1 (5)	0	21 (48)	CI, −5.4-−0.3	CI, −3.8-0.0
Increased, no. pt (%)	0	4 (20)	8 (18)	P = .01 (signed-rank	P > .10 (signed-rank
Decreased, no. pt (%)	21 (95)	16 (80)	15 (34)	test)	test)
	(data for 22 patients)	(data for 20 patients)	(data for 44 patients)	(data for 15 patients)	(data for 15 patients)
^{131}I uptake (24 hr)					
Mean (%)	64 ± 16	61 ± 21			
Median (%)	65	63			
Range (%)	15-92	12-92			
Normal, no. pt (%)	1 (1)	5 (9)			
Increased, no. pt (%)	82 (99)	51 (91)			
	(data for 83 patients)	(data for 56 patients)			

TABLE XIV: LABORATORY TEST RESULTS AT DIAGNOSIS OF THYROID DYSFUNCTION AND OF OPHTHALMOPATHY AND AT FINAL EXAMINATION AMONG 108 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY WITH HYPERTHYROIDISM (CONT'D)

TEST	AT DIAGNOSIS OF		AT FINAL EXAMINATION	DIFFERENCE BETWEEN VALUE AT DIAGNOSIS AND FINAL EXAMINATION	
	THYROID DYSFUNCTION	GO		THYROID DIAGNOSIS	GO DIAGNOSIS
Thyroid-stimulating immunoglobulins (TSI)					
Mean (TSI index)	7.2 ± 4.3	8.7 ± 6.5			
Median (TSI index)	7.8	8.3			
Range (TSI index)	1.3-12	0.9-20			
Normal, no. pt (%)	1 (12)	1 (8)			
Increased, no. pt (%)	7 (88)	11 (92)			
	(data for 8 patients)	(data for 12 patients)			
Microsomal antibody titer					
Median	1:1,000	1:6,400			
Range	1:100-1:25,600	1:100-1:25,600			
Increased, no. pt (%)	10 (100)	10 (100)			
	(data for 10 patients)	(data for 10 patients)			
Thyroglobulin antibody titer					
Median	1:100	1:100			
Range	Undetectable to 1:100	Undetectable to 1:100			
Normal, no. pt (%)	4 (44)	4 (57)			
Increased, no. pt (%)	5 (56)	3 (43)			
	(data for 9 patients)	(data for 7 patients)			
Fine-needle aspiration biopsy of thyroid	No data	No data			

CI, confidence interval; GO, Graves' ophthalmopathy.

years of the study period, but more recently they have been supplanted by the sensitive thyroid-stimulating hormone (sTSH) test. At the time of diagnosis of thyroid dysfunction, the mean values for the TSH and sTSH, respectively, were 0.62 μU/ml and 0.51 mIU/l; because of the wide range of results for these tests, however, the median values may provide more useful information (0.3 μU/ml and 0.05 mIU/l, respectively). At the time of diagnosis of ophthalmopathy, often later in the patient's clinical course when hyperthyroidism had been treated, the average and median values for TSH and sTSH were closer to the normal range. The uptake of ^{131}I was increased at the diagnosis of both thyroid dysfunction and GO. The detection of thyroid-stimulating immunoglobulins (TSI) by a cyclic AMP assay in FRTL5 cells is an excellent test (and currently the laboratory determination of choice) to demonstrate abnormal thyroid stimulation, but this was available only during the last portion of the study period. In the few patients in whom it was obtained, the results were markedly abnormal both at the time of diagnosis of thyroid dysfunction and at the time of diagnosis of GO (average TSI indices of 6.5 and 7.6, respectively).

Long-term monitoring of the thyroid status of patients with thyroid dysfunction typically involves serial measurements of total thyroxine, sTSH, or both.[91] Because the many tests that were obtained at the time of diagnosis were performed in only a few patients at their most recent follow-up examinations, the values were omitted from Tables XIII and XIV.

The average and median total serum thyroxine level was 8.6 μg/dl in the 71 patients in whom data were available at most recent follow-up. The difference between the thyroxine level at the time of diagnosis of thyroid dysfunction and at final examination was significant ($P = .0001$; signed-rank test), as was the difference in values obtained at diagnosis of ophthalmopathy and at the most recent follow-up ($P = .0001$; signed-rank test).

Among the 47 patients in whom the sTSH level was available, the average value was 4.6 mIU/l and the median was 1.2. The difference between the values at diagnosis of thyroid dysfunction and at most recent follow-up was significant ($P \leq .01$; signed-rank test), whereas the difference between sTSH at diagnosis of ophthalmopathy and at final examination did not attain statistical significance ($P > .10$; signed-rank test). Follow-up TSH values were available for only 17 patients from the earlier years of the study; although the mean level was 15.4 μU/ml, the median value was 3.4. These data are skewed because patients treated with radioactive iodine routinely are examined 3 months after therapy, when the TSH levels are increased. The levels may or may not be checked at subsequent visits.

Laboratory test values for the 108 patients with hyperthyroidism are outlined in Table XIV and are in accordance with expectations for this subgroup of thyroid dysfunction.

TREATMENT OF THYROID DYSFUNCTION

The different types and sequelae of treatment for thyroid dysfunction are summarized in Table XV. Overall, 110 (91.7%) of the 120 incident cases had one or more forms of therapy. Among the 108 patients who were hyperthyroid, 42 (38.9%) were treated at some point in their course with oral medication (methimazole, propylthiouracil, iodides, or β-adrenergic blockers), 96 patients (88.9%) were treated with radioactive iodine to ablate the thyroid gland, and 7 patients (6.5%) underwent subtotal thyroidectomy.

The mean, median, and range of intervals between radioiodine therapy or thyroidectomy and the diagnosis of ophthalmopathy varied widely. For example, the average interval between ^{131}I treatment and diagnosis of GO was 402 days (1.1 years), whereas the median was 0 days. The range for this interval was 6.8 years before radioiodine therapy to 29.2 years after treatment. Similarly, in relation to subtotal thyroidectomy, the average interval between operation and GO diagnosis was 14.5 years, whereas the median

TABLE XV. TREATMENT OF THYROID DYSFUNCTION AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY

THERAPY	NO.	%
For thyroid dysfunction (all types)	110	91.7
For hyperthyroidism (108 patients)		
Medical: methimazone, propylthiouracil, iodides, or β-adrenergic block	42	38.9
^{131}I	96	88.9
Age at treatment (yr)		
Mean, 44.7 ± 16.8		
Median, 43.2		
Range, 14.7-88.7		
Number of treatments		
One	88	91.7
Dose (mCi)		
Mean, 11.7		
Median, 11		
Range, 3-29		
Two	7	7.2
Dose (mCi)		
Mean, 20.3		
Median, 1.5		
Range, 13-36		
Three	1	1.0
Dose (20 mCi)		
Interval from initial treatment until diagnosis of GO (yr)		
Mean, 1.1 ± 4.1		
Median, 0		
Range, −6.8-29.2		

TABLE XV: TREATMENT OF THYROID DYSFUNCTION AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY (CONT'D)

THERAPY	NO.	%
Relationship of ^{131}I therapy with ophthalmopathy*		
Signs and symptoms improved (time determined for 17 patients)	20/71	28.2
Immediately	2/17	11.8
≤3 mo	6/17	35.3
≤6 mo	6/17	35.3
>6 mo	3/17	17.6
Signs and symptoms unchanged	33/71	46.5
Signs and symptoms worsened (time determined for 14 patients)	18/71	25.4
Immediately	4/14	28.6
≤3 mo	6/14	42.9
≤6 mo	4/14	28.6
Thyroidectomy (subtotal)	7	6.5
Age at operation (yr)		
Mean, 35.4 ± 23.1		
Median, 25.7		
Range, 13.6-70.9		
Interval until diagnosis of GO (yr)		
Mean, 14.5 ± 24.0		
Median, 0.56		
Range, −4.6-62.7		
Hypothyroidism after treatment of hyperthyroidism		
Following ^{131}I (n=97)	90	92.8
Following thyroidectomy (n=7)	4	57.1
Interval until onset of hypothyroidism (yr) (data for 87 patients)		
Mean, 0.4 ± 1.4		
Median, 0.3		
Range, −5.8-7.3		
Initial replacement dose of thyroxine (mg) (data for 61 patients)		
Mean, 0.13		
Median, 0.15		
Range, 0.05-0.2		
Frequency of thyroid replacement hormone use at last follow-up		
All patients (n=120)	91	75.8
Hyperthyroid patients (n=108)	87	80.6

*Combined data for 71 patients from chart review and patient assessment with questionnaire.

interval was slightly more than 6 months. The range between thyroid surgery and ophthalmopathy also was wide; it extended from 4.6 years before the diagnosis of GO to, in one patient (a lifelong resident of the community whose eye status was well documented), more than 60 years

from the date of subtotal thyroidectomy. Of the 7 patients who underwent thyroidectomy, in 2 ophthalmopathy developed before operation (1,664 days and 526 days) and in 5 eye signs and symptoms developed postoperatively (ophthalmopathy diagnosed 129 days, 203 days, 7,952 days, 8,031 days, and 22,894 days after operation).

The relationship of ophthalmopathy to ^{131}I therapy was determined for 71 patients. Eye signs and symptoms did not appear to change in 33 patients (46.5%), improved after radioactive iodine in 20 patients (28.2%), and seemed to worsen after therapy in 18 patients (25.4%). The time courses for changes in ophthalmopathy are outlined in Table XV.

Hypothyroidism developed after therapy for hyperthyroidism in 90 (92.8%) of the 97 patients who were treated with ^{131}I and in 4 (57.1%) of the 7 patients who underwent subtotal thyroidectomy. The intervals until the onset of hypothyroidism, the initial replacement dose of thyroid hormone, and the frequency of use of thyroxine products are summarized in Table XV.

The cumulative probabilities of treatment with radioactive iodine or subtotal thyroidectomy among the 108 patients with hyperthyroidism are illustrated in Figs 7 and 8 and summarized in Tables XVI and XVII, respectively. Twenty-one patients were treated with ^{131}I on the same day that hyperthyroidism was diagnosed, and 46 patients had undergone treatment by the end of the first week. The cumulative probability of radioactive iodine therapy was 64.8% ± 9.2% after 1 month and 76.9% ± 8.1% after 6 months. At our institution, where surgical therapy for hyperthyroidism has been used infrequently during the past 2 decades, the probability of having undergone subtotal thyroidectomy was 5.6% ± 4.3% at 1 year and 7.7% ± 5.1% at 5 and 10 years.

OPHTHALMIC SYMPTOMS AND SIGNS AT DIAGNOSIS OF GRAVES' OPHTHALMOPATHY

The symptoms and signs that were recorded at the diagnosis of ophthalmopathy among the 120 incident cases are outlined in Table XVIII; these data are presented graphically in Figs 9 and 10. Nine patients (7.5%) noted blurred vision; it involved both eyes in seven patients (5.8%) and was unilateral in the remaining two patients. Of the 20 patients (16.7%) who had diplopia, double vision was intermittent and present only during fatigue in 4 patients (3.3%), noted only in extremes of gaze in 9 patients (7.5%), constant but correctable by prisms in 3 patients (2.5%), and constant and unresolvable by prisms in 4 patients (3.3%). Twenty-five patients (20.8%) had lacrimation; tearing involved both eyes in 18 patients (15%), the right eye only in 5 patients (4.2%), and the left eye only in 2 patients (1.7%). Pain or ocular discomfort was experienced by 36 patients (30%); the symptom

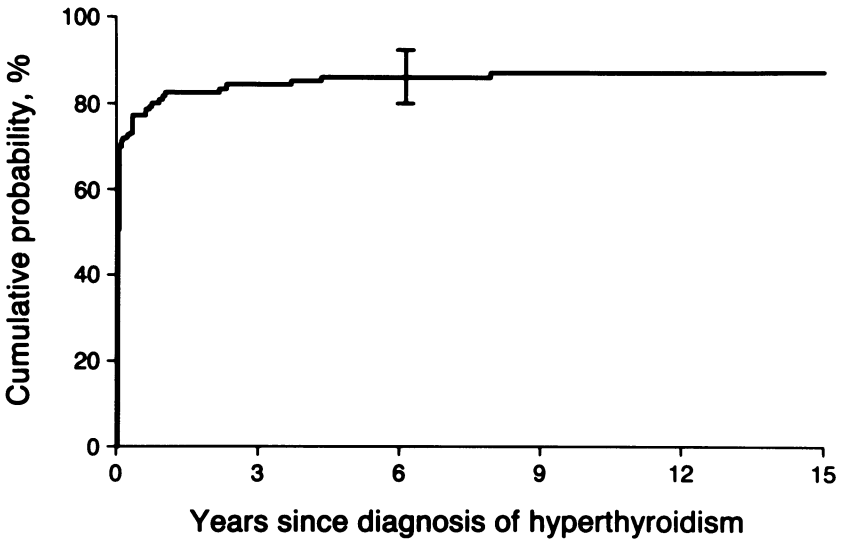

FIGURE 7
Cumulative probability of therapy with radioactive iodine among 108 patients with hyperthyroidism (estimate with 95% confidence interval).

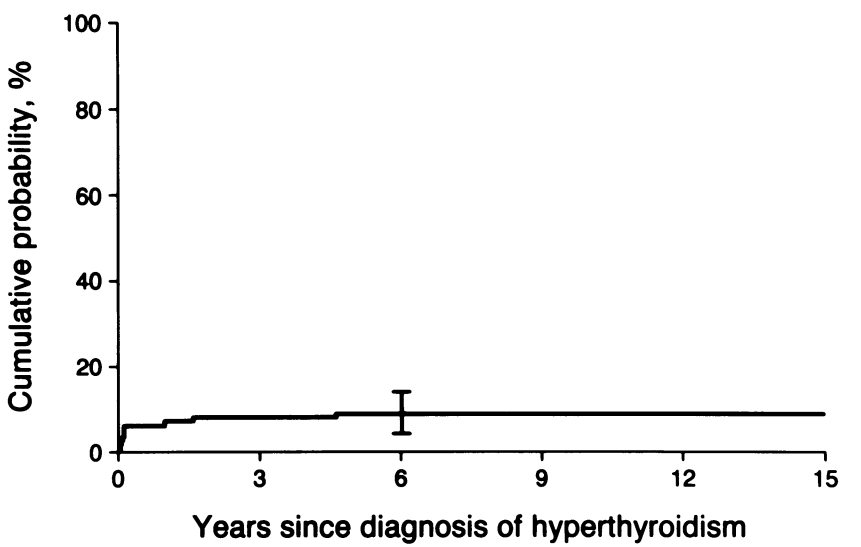

FIGURE 8
Cumulative probability of subtotal thyroidectomy among 108 patients with hyperthyroidism (estimate with 95% confidence interval).

TABLE XVI: CUMULATIVE PROBABILITY OF THERAPY WITH RADIOACTIVE IODINE AMONG 108 PATIENTS WITH HYPERTHYROIDISM

INTERVAL SINCE DIAGNOSIS OF HYPERTHYROIDISM	NO. OF PATIENTS STILL AT RISK	PROBABILITY ± SE (%)
1 wk	62	42.6 ± 9.5
1 mo	38	64.8 ± 9.2
6 mo	24	76.9 ± 8.1
1 yr	19	81.7 ± 7.3
2 yr	18	82.6 ± 7.2
3 yr	16	84.6 ± 6.9
4 yr	15	85.5 ± 6.7
5 yr	14	86.5 ± 6.5
10 yr	10	87.6 ± 6.3

SE, standard error.

TABLE XVII: CUMULATIVE PROBABILITY OF SUBTOTAL THYROIDECTOMY AMONG 108 PATIENTS WITH HYPERTHYROIDISM

INTERVAL SINCE DIAGNOSIS OF HYPERTHYROIDISM (YR)	NO. OF PATIENTS STILL AT RISK	PROBABILITY ± SE (%)
1	101	5.6 ± 4.3
2	98	6.5 ± 4.7
3	93	6.5 ± 4.7
4	84	6.5 ± 4.7
5	78	7.7 ± 5.1
10	53	7.7 ± 5.1

SE, standard error.

affected both eyes in 26 patients (21.7%), the right eye only in 7 patients (5.8%), and the left eye only in 3 patients (2.5%). Nineteen patients (15.8%) complained of light sensitivity; in all but two cases photophobia was bilateral.

The interval between the onset of eye symptoms and the diagnosis of GO was determined for 78 patients. The average interval was 220 ± 1,077 days, the median was 45 days, and range was 2.8 years before diagnosis to 24.8 years after diagnosis.

Quantitation of visual acuity was recorded for 111 patients. Best corrected acuity of 20/20 or better was noted in 93 right and left eyes (83.8%). Decreased vision attributable to Graves' optic neuropathy involved only four eyes (1.8% of eyes), resulting in acuities of 20/25, 20/40 (two eyes), and 20/100.

TABLE XVIII: SYMPTOMS AND SIGNS AT DIAGNOSIS OF GRAVES' OPHTHALMOPATHY AMONG 120 INCIDENT CASES

FEATURE	NO.		%
Blurred vision			
Right eye only	1		0.8
Left eye only	1		0.8
Both eyes	7		5.8
Diplopia	20		16.7
Present only when fatigued	4	3.3	
Present in extremes of gaze	9	7.5	
Constant but correctable by prisms	3	2.5	
Constant and not correctable by prisms	4	3.3	
Lacrimation			
Right eye only	5		4.2
Left eye only	2		1.7
Both eyes	18		15.0
Pain or ocular discomfort			
Right eye only	7		5.8
Left eye only	3		2.5
Both eyes	26		21.7
Photophobia			
Right eye only	1		0.8
Left eye only	1		0.8
Both eyes	17		14.2
Visual acuity (data for 111 patients)			
Right eye			
20/15	3		2.7
20/20	90		81.1
20/25	8		7.2
20/30	3		2.7
20/40	4*		3.6
20/60	2†		1.8
20/100	1‡		0.9
Left eye			
20/15	3		2.7
20/20	90		81.1
20/25	10§		9.0
20/30	3		2.7
20/40	4//		3.6
Hand motions	1¶		0.9
Visual field defect (demonstrated by perimetry)			
Right eye			
Generalized depression	1		0.8
Superior altitudinal defect	1		0.8
Left eye			
Generalized depression	1		0.8
Superior altitudinal defect	1		0.8
Color vision defect			
Right eye			
Inherited dyschromatopsia	2		1.7
Graves' optic neuropathy	1		0.8
Left eye			
Inherited dyschromatopsia	2		1.7
Graves' optic neuropathy	1		0.8

TABLE XVIII: SYMPTOMS AND SIGNS AT DIAGNOSIS OF GRAVES' OPHTHALMOPATHY AMONG 120 INCIDENT CASES (CONT'D)

FEATURE	NO.	%
Eyelid retraction		
Upper eyelids (data for 111 patients)		
Right upper eyelid only	13	11.7
Left upper eyelid only	11	9.9
Both upper eyelids	61	55.0
Right upper eyelid		
Amount (mm)		
Mean, 2.2 ± 1.0		
Median, 2		
Range, 1-4		
Grade		
Mild (<2 mm)	47	42.3
Moderate (2-4 mm)	27	24.3
Severe (>4 mm)	0	0
Left upper eyelid		
Amount (mm)		
Mean, 2.0 ± 1.0		
Median, 2		
Range, 1-5		
Grade		
Mild (<2 mm)	46	41.4
Moderate (2-4 mm)	25	22.5
Severe (>4 mm)	1	0.9
Lower eyelids (data for 102 patients)		
Right lower eyelid only	0	0
Left lower eyelid only	2	2.0
Both lower eyelids	22	21.6
Right lower eyelid		
Amount (mm)		
Mean, 1.8 ± 0.8		
Median, 2		
Range, 1-3		
Grade		
Mild (<2 mm)	13	12.7
Moderate (2-4 mm)	8	7.8
Severe (>4 mm)	0	0
Left lower eyelid		
Amount (mm)		
Mean, 2.0 ± 0.9		
Median, 2		
Range, 1-3		
Grade		
Mild (<2 mm)	13	12.7
Moderate (2-4 mm)	11	10.8
Severe (>4 mm)	0	0
Eyelid fissure (mm)		
Right		
Mean, 10.9 ± 2.3		
Median, 11		
Range, 7-15		

TABLE XVIII: SYMPTOMS AND SIGNS AT DIAGNOSIS OF GRAVES' OPHTHALMOPATHY AMONG 120 INCIDENT CASES (CONT'D)

FEATURE	NO.	%
Left		
Mean, 11.1 ± 2.4		
Median, 10.5		
Range, 6-18		
Lagophthalmos (data for 102 patients)		
Right eyelids only	2	2.0
Left eyelids only	3	2.9
Both right and left eyelids	8	7.8
Right eyelids		
Grade		
Mild (<2 mm)	8	7.8
Moderate (2-4 mm)	2	2.0
Severe (>4 mm)	0	0
Left eyelids		
Grade		
Mild (<2 mm)	9	8.8
Moderate (2-4 mm)	2	2.0
Severe (>4 mm)	0	0
Lid lag (data for 105 patients)		
Right upper eyelid only	9	8.6
Left upper eyelid only	6	5.7
Both upper eyelids	37	35.2
Eyelid fullness (data for 117 patients)		
Right eyelids only	3	2.6
Left eyelids only	4	3.4
Both right and left eyelids	31	26.5
Right eyelids		
Grade		
Mild	27	23.1
Moderate	6	5.1
Severe	1	0.9
Left eyelids		
Grade		
Mild	26	22.2
Moderate	8	6.8
Severe	1	0.9
Exophthalmometry (mm) (data for 111 patients)		
Right eye		
Mean, 18.8 ± 2.6		
Median, 18		
Range, 12-26		
Left eye		
Mean, 18.9 ± 2.9		
Median, 19		
Range, 11-26		
Corneal staining (data for 108 patients)		
Right eye only	1	0.9
Left eye only	1	0.9
Both eyes	9	8.3

TABLE XVIII: SYMPTOMS AND SIGNS AT DIAGNOSIS OF GRAVES' OPHTHALMOPATHY AMONG 120 INCIDENT CASES (CONT'D)

FEATURE	NO.	%
Superior limbic keratoconjunctivitis (data for 109 patients)		
Right eye only	0	0
Left eye only	0	0
Both eyes	1	0.9
Conjunctival injection (data for 116 patients)		
Right eye only	3	2.6
Left eye only	2	1.7
Both eyes	35	30.2
Chemosis (data for 116 patients)		
Right eye only	2	1.7
Left eye only	1	0.9
Both eyes	24	20.7
Extraocular muscle dysfunction (data for 116 patients)		
Right eye only	5	4.3
Left eye only	4	3.4
Both eyes	21	18.1
Resistance of globe to retropulsion (data for 46 patients)		
Right eye only	1	2.2
Left eye only	2	4.3
Both eyes	11	23.9
Intraocular pressure (mm Hg) (data for 92 patients)		
Right eye		
Mean, 16.4 ± 3.2		
Median, 16		
Range, 8-27		
Left eye		
Mean, 16.2 ± 3.4		
Median, 16		
Range, 10-29		
Optic disk appearance (data for 114 patients)		
Right eye only		
Choked	1	0.9
Pale	1	0.9
Left eye only		
Choked	0	0
Pale	0	0
Both eyes	0	0
Choroidal folds (data for 108 patients)		
Right eye only	0	0
Left eye only	0	0
Both eyes	0	0

*One patient with Graves' optic neuropathy, two patients had cataracts, and one patient had Fuchs' corneal dystrophy.
†Both patients had cataracts.
‡Patient had Graves' optic neuropathy.
§One patient had Graves' optic neuropathy.
//One patient had Graves' optic neuropathy, one patient had cataract, one patient cataract and Fuch's corneal dystrophy, and one patient had Fuch's corneal dystrophy.
¶Patient had cataract.

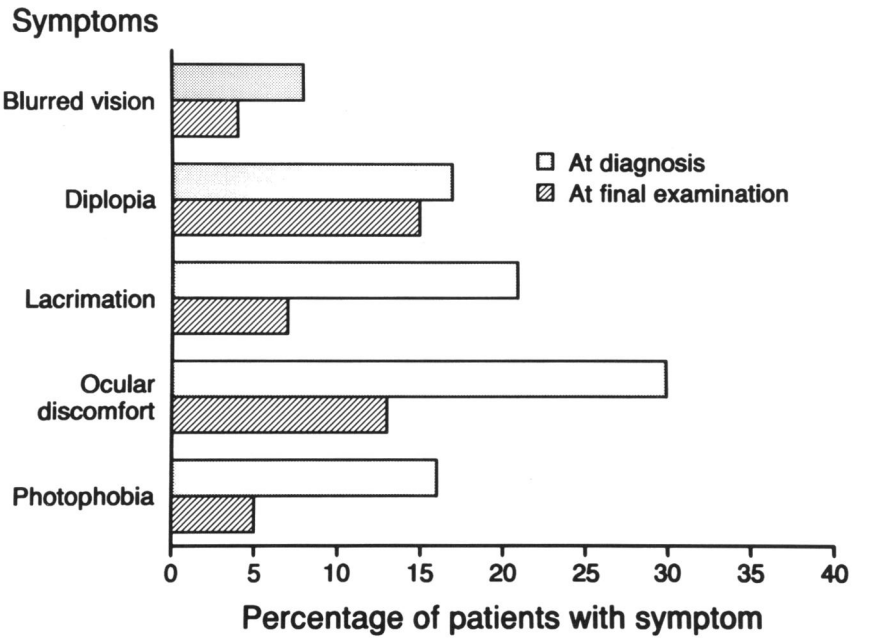

FIGURE 9
Symptoms of Graves' ophthalmopathy at diagnosis and at final examination in 120 incident cases. (Numerical data are reported in Tables XVIII and XIX.)

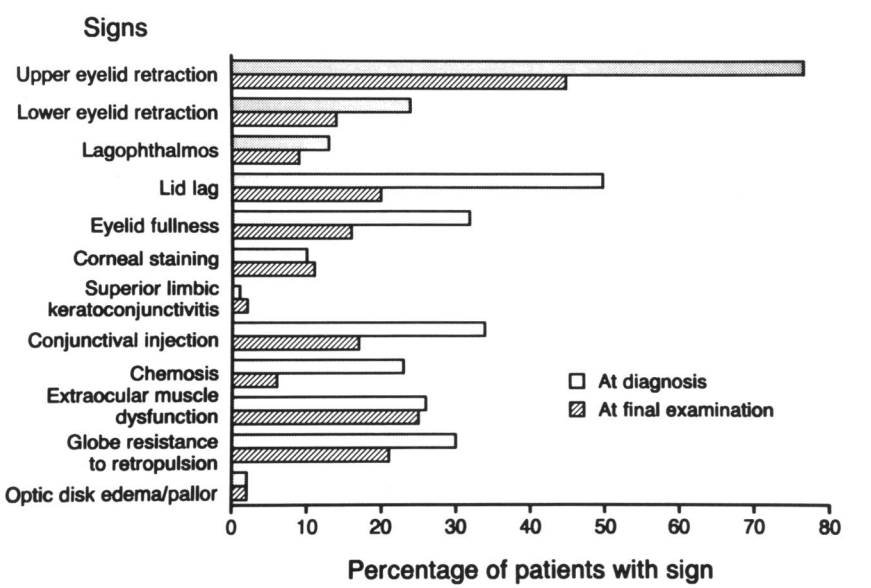

FIGURE 10
Signs of Graves' ophthalmopathy at diagnosis and at final examination in 120 incident cases. (Numerical data are reported in Tables XVIII and XIX.)

Formal perimetry was performed in only two patients at the time of diagnosis of ophthalmopathy; one patient demonstrated generalized depression of the visual field in each eye, whereas the other patient had bilateral superior altitudinal defects. Color vision was tested in only 20 patients; abnormal results attributable to GO were documented in each eye of one patient.

Bilateral upper eyelid retraction was present in 61 (55%) of the 111 patients for whom data were available, and an additional 24 patients had either right (13 patients; 11.7%) or left (11 patients; 9.9%) upper eyelid retraction. The average amount of retraction was 2.2 and 2.0 mm for the right and left upper eyelids, respectively, with ranges from 1 to 5 mm. Retraction of the right upper eyelid was graded as mild (< 2 mm) in 47 instances (42.3%) and moderate (2 to 4 mm) in 27 cases (24.3%), whereas the grade of retraction for the left upper eyelid was mild in 46 lids (41.4%), moderate in 25 instances (22.5%), and severe in 1 case (0.9%). Lower eyelid retraction was bilateral in 22 (21.6%) of 102 patients and affected the left lower lid only in 2 cases (2%); no patient had isolated right lower lid retraction. The average degree of retraction was 1.8 mm for right lower lids and 2 mm for left lower lids, with ranges from 1 to 3 mm. Lower eyelid retraction was mild for both lower eyelids in 13 cases (12.7%) and moderate for 8 right lower eyelids (7.8%) and 11 left lower eyelids (10.8%). The average eyelid fissure was 10.9 mm (range, 7 to 15 mm) for right eyes and 11.1 mm (range, 6 to 18 mm) for left eyes.

Lagophthalmos was documented in 13 (12.7%) of 102 patients; it was bilateral in 8 patients and unilateral in the remaining 5. The degree of lagophthalmos was mild (< 2 mm) for the right eyelids of 8 patients and the left eyelids of 9 patients and was moderate (2 to 4 mm) in 2 patients for both the right and the left eyes.

Lid lag was noted in 52 (49.5%) of 105 patients; the sign was bilateral in 37 patients (35.2%), affected the right upper eyelid only in 9 patients (8.6%), and involved the left upper eyelid only in 6 cases (5.7%).

Eyelid fullness from edema and prolapsed orbital fat or lacrimal gland tissue was present bilaterally in 31 (26.5%) of 117 patients and affected either the right or left eyelids in an additional 7 patients. The degree of fullness was graded as mild in about 75% to 80% of eyelids that demonstrated the feature, and only one patient in the incident cohort (0.9%) had bilateral severe eyelid fullness.

Exophthalmometry measurements were available for 111 of the 120 incident cases at the time of diagnosis of GO. The averages for the right and left eyes, respectively, were 18.8 mm (range, 12 to 26) and 18.9 mm (range, 11 to 26).

Corneal staining with either fluorescein or rose bengal was noted in 11 patients (10.2%), among whom 9 had the finding bilaterally. Superior limbic keratoconjunctivitis was documented in only 1 of 109 patients (0.9%), and the finding was bilateral. Conjunctival injection, either diffuse or isolated over the insertions of the horizontal rectus muscles, was present in 40 (34.5%) of 116 patients; the sign was bilateral in 35 cases. Conjunctival edema was present in slightly fewer patients; chemosis was present bilaterally in 24 (20.7%) of 116 patients and was unilateral in an additional 3 patients.

Extraocular muscle dysfunction was documented at the time of diagnosis of GO in 30 of 116 patients (25.9%). Both eyes were involved in 21 cases (18.1%), whereas unilateral restriction of ductions was noted in 9 patients.

Comments regarding resistance of the globe to retropulsion were recorded in a minority of patients (46 of the 120). Among these cases, the sign was documented in 14 patients (30.4%).

Intraocular pressure measurements in primary gaze were available for 92 patients. The average pressure was 16.4 mm (range, 8 to 27) for right eyes and 16.2 mm (range, 10 to 29) for left eyes. Because intraocular pressures were measured in upgaze, downgaze, or both in only a few patients, these data are not included in this report.

Results of ophthalmoscopy were normal in 112 of 114 patients. One patient had a choked right optic disk and another patient had optic disk pallor. Choroidal folds were not documented in any patient at the time of diagnosis of GO.

OPHTHALMIC SYMPTOMS AND SIGNS AT THE FINAL EXAMINATION

Twenty-one patients were not examined after the initial visit, but information on symptoms and signs at the most recent examination for the remaining 99 patients is outlined in Table XIX; these data are presented graphically in Figs 9 and 10. The symptoms and signs for which the frequencies in affected eyes differed significantly between the first and last examinations are summarized in Tables XX and XXI (described in more detail below).

Blurred vision was described in both eyes by three patients and in the left eye only in one patient. Double vision was noted by 15 patients: it was present only during fatigue in 2 patients, intermittent and present only in extremes of gaze in 6 patients, and constant but correctable with prism glasses in 7 patients. No patient had diplopia that could not be corrected with prisms. Seven patients had lacrimation, 13 patients described pain or ocular discomfort, and 5 patients had sensitivity to light.

Visual acuity was documented for 94 patients. Best corrected vision of 20/20 was recorded for 77 right eyes (81.9%) and 74 left eyes (78.7%).

TABLE XIX: SYMPTOMS AND SIGNS OF GRAVES' OPHTHALMOPATHY AT FINAL EXAMINATION*

FEATURE	NO.		%
Blurred vision			
Right eye only		0	0
Left eye only		1	1.0
Both eyes		3	3.0
Diplopia		15	15.2
Present only when fatigued	2	2.0	
Present in extremes of gaze	6	6.1	
Constant but correctable by prisms	7	7.1	
Constant and not correctable by prisms	0	0	
Lacrimation			
Right eye only		0	0
Left eye only		0	0
Both eyes		7	7.1
Pain or ocular discomfort			
Right eye only		4	4.0
Left eye only		0	0
Both eyes		9	9.1
Photophobia			
Right eye only		0	0
Left eye only		0	0
Both eyes		5	5.1
Visual acuity (data for 94 patients)			
Right eye			
20/20		77	81.9
20/25		4	4.3
20/30		5†	5.3
20/40		1‡	1.1
20/50		3§	3.2
20/60		3//	3.2
20/400		1¶	1.1
Left eye			
20/20		74	78.7
20/25		9	9.6
20/30		3	3.2
20/40		5#	5.3
20/50		1°°	1.1
20/80		1††	1.1
Light projection		1‡‡	1.1
Visual field defect (demonstrated by perimetry)			
Right eye			
Generalized depression		2	2.0
Central scotoma		1	1.0
Left eye			
Generalized depression		2	2.0
Inferior depression		1	1.0
Color vision defect (no data)			
Eyelid retraction			
Upper eyelids (data for 87 patients)			
Right upper eyelid only		8	9.1
Left upper eyelid only		5	5.7

TABLE XIX: SYMPTOMS AND SIGNS OF GRAVES' OPHTHALMOPATHY AT FINAL EXAMINATION* (CONT'D)

FEATURE	NO.	%
Both upper eyelids	26	29.9
Right upper eyelid		
Amount (mm)		
Mean, 3.0 ± 1.7		
Median, 3		
Range, 1-8		
Grade		
Mild (<2 mm)	16	18.4
Moderate (2-4 mm)	16	18.4
Severe (>4 mm)	2	2.3
Left upper eyelid		
Amount (mm)		
Mean, 2.7 ± 1.8		
Median, 2		
Range, 1-9		
Grade		
Mild (<2 mm)	14	16.1
Moderate (2-4 mm)	16	18.4
Severe (>4 mm)	1	1.1
Lower eyelids (data for 84 patients)		
Right lower eyelid only	1	1.2
Left lower eyelid only	2	2.4
Both lower eyelids	9	10.7
Right lower eyelid		
Amount (mm)		
Mean, 1.9 ± 0.7		
Median, 2		
Range, 1-3		
Grade		
Mild (<2 mm)	6	7.1
Moderate (2-4 mm)	4	4.8
Severe (>4 mm)	0	0
Left lower eyelid		
Amount (mm)		
Mean, 1.7 ± 0.5		
Median, 2		
Range, 1-2		
Grade		
Mild (<2 mm)	7	8.3
Moderate (2-4 mm)	4	4.8
Severe (>4 mm)	0	0
Eyelid fissure (mm)		
Right		
Mean, 10.7 ± 2.1		
Median, 11		
Range, 5-15		
Left		
Mean, 10.9 ± 2.5		
Median, 11		
Range, 6-18		

TABLE XIX: SYMPTOMS AND SIGNS OF GRAVES' OPHTHALMOPATHY AT FINAL EXAMINATION* (CONT'D)

FEATURE	NO.	%
Lagophthalmos (data for 85 patients)		
Right eyelids only	2	2.4
Left eyelids only	0	0
Both right and left eyelids	6	7.1
Right eyelids		
Grade		
Mild (<2 mm)	7	8.2
Moderate (2-4 mm)	1	1.2
Severe (>4 mm)	0	0
Left eyelids		
Grade		
Mild (<2 mm)	5	5.9
Moderate (2-4 mm)	1	1.2
Severe (>4 mm)	0	0
Lid lag (data for 81 patients)		
Right upper eyelid only	4	4.9
Left upper eyelid only	1	1.2
Both upper eyelids	11	13.6
Eyelid fullness (data for 117 patients)		
Right eyelids only	1	1.1
Left eyelids only	3	3.4
Both right and left eyelids	10	11.5
Right eyelids		
Grade		
Mild	9	10.3
Moderate	2	2.3
Severe	0	0
Left eyelids		
Grade		
Mild	10	11.5
Moderate	2	2.3
Severe	1	1.1
Exophthalmometry (mm) (data for 67 patients)		
Right eye		
Mean, 19.2 ± 2.8		
Median, 19		
Range, 12-25		
Left eye		
Mean, 19.7 ± 3.0		
Median, 20		
Range, 11-25		
Corneal staining (data for 89 patients)		
Right eye only	2	2.2
Left eye only	1	1.1
Both eyes	7	7.9
Superior limbic keratoconjunctivitis (data for 88 patients)		
Right eye only	0	0
Left eye only	0	0
Both eyes	2	2.3

TABLE XIX: SYMPTOMS AND SIGNS OF GRAVES' OPHTHALMOPATHY AT FINAL EXAMINATION* (CONT'D)

FEATURE	NO.	%
Conjunctival injection (data for 94 patients)		
Right eye only	1	1.1
Left eye only	0	0
Both eyes	15	16.0
Chemosis (data for 95 patients)		
Right eye only	1	1.1
Left eye only	1	1.1
Both eyes	4	4.2
Extraocular muscle dysfunction (data for 97 patients)		
Right eye only	2	2.1
Left eye only	1	1.0
Both eyes	21	21.6
Resistance of globe to retropulsion (data for 33 patients)		
Right eye only	1	3.0
Left eye only	1	3.0
Both eyes	5	15.2
Intraocular pressure (mm Hg) (data for 79 patients)		
Right eye		
Mean, 16.5 ± 2.7		
Median, 16		
Range, 11-23		
Left eye		
Mean, 16.6 ± 2.7		
Median, 17		
Range, 11-24		
Optic disk appearance (data for 89 patients)		
Right eye only		
Choked	0	0
Pale	1	1.1
Left eye only		
Choked	0	0
Pale	0	0
Both eyes		
Pale	1	1.1
Choroidal folds (data for 86 patients)		
Right eye only	0	0
Left eye only	0	0
Both eyes	0	0

*Data are for 99 of 120 patients; 21 patients were not examined after initial visit.
†One patient had Graves' optic neuropathy.
‡Patient had cataract.
§One patient had cataract, one patient had macular degeneration, and one patient had cataract and Fuchs' corneal dystrophy.
//One patient had Graves' optic neuropathy and cataract, one patient cataract and macular degeneration, and one patient had cataract.
¶Patient had macular degeneration.
#Four patients had cataracts, one patient had macular degeneration.
**Patient had Fuchs' corneal dystrophy.
††Patient had macular degeneration.
‡‡Patient had cataract and macular degeneration.

TABLE XX: OPHTHALMIC SYMPTOMS AND SIGNS: STATISTICALLY SIGNIFICANT DIFFERENCES IN FREQUENCIES IN AFFECTED EYES FROM INITIAL TO FINAL EXAMINATIONS (ENTIRE INCIDENCE COHORT OF 120 PATIENTS)

SYMPTOM OR SIGN*	*P* VALUE	STATISTICAL TEST
Lacrimation		
Right eye	0.0015	Sign
Left eye	0.0075	Sign
Pain or ocular discomfort		
Right eye	0.0015	Sign
Left eye	0.0005	Sign
Photophobia		
Right eye	0.0023	Sign
Left eye	0.0023	Sign
Eyelid retraction		
Right upper eyelid	0.0119	Signed-rank
Left upper eyelid	0.0027	Signed-rank
Lid lag		
Right upper eyelid	0.0015	Sign
Left upper eyelid	0.0002	Sign
Eyelid fullness		
Right eyelids	0.0058	Signed-rank
Left eyelids	0.0073	Signed-rank
Conjunctival injection		
Right eye	0.0025	Sign
Left eye	0.0009	Sign
Chemosis		
Right eye	0.0015	Sign
Left eye	0.0026	Sign
Exophthalmos		
Right eye	0.0037	Signed-rank
Left eye	0.0006	Signed-rank

*The frequency, grade, or amount of all symptoms and signs decreased from the initial to the final examination, with the exception of exophthalmos, which increased.

Decreased acuity attributable to GO was noted for the right eyes of two patients: 20/30 in one patient and 20/60 in the second patient (although the latter also had cataract that was thought to explain part of the visual impairment). Perimetry demonstrated generalized depression in both instances. Color vision testing was not performed at the final examination in any patient.

Bilateral upper eyelid retraction was documented in 39 of 87 patients; the eyelid malposition affected the right upper eyelid only in 8 patients (9.1%) and the left upper eyelid only in 5 patients (5.7%), and it was bilateral in 26 patients (29.9%). The average retraction of the right upper eyelid was 3 mm (range, 1 to 8), whereas the mean measurement for the left upper eyelid was

TABLE XXI: OPHTHALMIC SYMPTOMS AND SIGNS: STATISTICALLY SIGNIFICANT DIFFERENCES IN FREQUENCIES IN AFFECTED EYES FROM INITIAL TO FINAL EXAMINATIONS (96 PATIENTS WHO DID NOT UNDERGO OPHTHALMIC SURGICAL PROCEDURES)

SYMPTOM OR SIGN*	*P* VALUE	STATISTICAL TEST
Lacrimation		
Right eye	0.0010	Sign
Left eye	0.0039	Sign
Pain or ocular discomfort		
Right eye	0.0015	Sign
Left eye	0.0002	Sign
Photophobia		
Right eye	0.0117	Sign
Left eye	0.0215	Sign
Eyelid retraction		
Right upper eyelid	0.0111	Signed-rank
Left upper eyelid	0.0064	Signed-rank
Lid lag		
Right upper eyelid	0.0352	Sign
Left upper eyelid	0.0042	Sign
Eyelid fullness		
Right eyelids	0.0169	Signed-rank
Left eyelids	0.0347	Signed-rank
Chemosis		
Right eye	0.0127	Sign
Left eye	0.0213	Sign
Exophthalmos		
Right eye	0.0013	Signed-rank
Left eye	0.0005	Signed-rank

*The frequency, grade, or amount of all symptoms and signs decreased from the initial to the final examination, with the exception of exophthalmos, which increased.

2.7 mm (range, 1 to 9). The grade of right upper eyelid retraction was mild (< 2 mm) or moderate (2 to 4 mm) in 16 patients (18.4%) each and was severe (> 4 mm) in 2 patients (2.3%). The grade of left upper eyelid retraction was similar: mild in 14 patients (16.1%), moderate in 16 patients (18.4%), and severe in 1 patient (1.1%). Lower eyelid retraction was bilateral in 9 of 84 patients (10.7%), was isolated to the right lower eyelid only in 1 patient (1.2%), and involved the left lower eyelid alone in 2 patients (2.4%). The average amount of lower eyelid retraction was 1.9 mm (range, 1 to 3) and 1.7 mm (range, 1 to 2) for the right and left lower eyelids, respectively. Retraction was mild for six (7.1%) right lower eyelids and seven (8.3%) left lower eyelids and moderate for four (4.8%) right and four left lower lids. No patient had severe lower eyelid retraction at the most recent examination. The average right and left eyelid fissures were 10.7 mm (range,

5 to 15) and 10.9 mm (range, 6 to 18), respectively.

Lagophthalmos was present bilaterally in 6 (7.1%) of 85 patients and affected the right eyelids alone in an additional 2 patients (2.4%). The grade of lagophthalmos for right eyes was mild (< 2 mm) in seven patients (8.2%) and moderate (2 to 4 mm) in one patient (1.2%). Lagophthalmos was mild for the left eyelids in five patients (5.9%) and was moderate in 1 patient (1.2%).

Lid lag was documented bilaterally in 11 (13.6%) of 81 patients and was confined to either the right upper eyelid (4 patients, 4.9%) or the left upper eyelid (1 patient, 1.2%) in 5 patients.

Eyelid fullness was present in 14 patients: bilateral in 10 patients (11.5%), right eyelids only in 1 patient (1.1%), and left eyelids in 3 patients (3.4%). The degree of fullness was mild in nearly all cases, as outlined in Table XIX.

Exophthalmometry measurements were recorded for 67 patients at the final examination; the mean values were 19.2 mm and 19.7 mm for the right and left eyes, respectively (ranges, 12 to 25 and 11 to 25).

Corneal staining was bilateral in 7 (7.9%) of 89 patients; an additional 3 patients had unilateral staining. Superior limbic keratoconjunctivitis was documented bilaterally in 2 (2.3%) of 88 patients at final follow-up. Conjunctival injection was present in both eyes of 15 (16%) of 94 patients and was noted in the right eye only of 1 patient (1.1%). Chemosis was noted in 6 of 95 patients, and in 4 patients (4.2%) the edema affected both eyes.

Dysfunction of the extraocular muscles was noted bilaterally in 21 (21.6%) of 97 patients. Restriction of ductions was confirmed for the right eye only in two patients (2.1%) and for the left eye only in one patient (1%).

Resistance of the globe to retropulsion was documented in 7 (21.2%) of 33 patients; the finding was bilateral in 5 patients.

The average intraocular pressures in 79 patients were 16.5 mm Hg and 16.6 mm Hg for the right and left eyes, respectively. The range of values was 11 to 23 mm Hg for right eyes and 11 to 24 mm Hg for left eyes.

Comments about optic disk appearance were included in the records of 89 patients at last examination. Pallor was noted bilaterally in one patient (1.1%) and in the right eye only of one patient (1.1%). Choroidal folds were not documented in any patient during their clinical courses.

STATISTICALLY SIGNIFICANT CHANGES IN OPHTHALMIC SYMPTOMS AND SIGNS FROM INITIAL TO FINAL EXAMINATIONS

As outlined in Table XX, the frequencies of several ophthalmic symptoms and signs differed significantly between the time of diagnosis of GO and the most recent follow-up examination among the entire incidence cohort. The pertinent symptoms included lacrimation, pain or ocular discomfort, and

photophobia. Signs that changed significantly over time included eyelid retraction, lid lag, eyelid fullness, conjunctival injection, chemosis, and exophthalmos. The changes in frequencies of the remaining symptoms and signs recorded in Tables XVIII and XIX did not achieve statistical significance.

In addition to the entire incidence cohort, patients who did not undergo surgical treatment for GO (n = 96) were analyzed separately. As outlined in Table XXI, statistically significant changes in the frequencies of symptoms and signs occurred for all of the variables noted above for the entire cohort, except for conjunctival injection.

For both groups analyzed, the frequency, grade, or amount of all symptoms and signs decreased (or clinically improved) from the initial to the final examination, with the exception of exophthalmos, which increased. Changes in exophthalmometry measurements for the entire incidence cohort (including patients who underwent orbital decompression) are illustrated in Fig 11.

TREATMENT OF GRAVES' OPHTHALMOPATHY

As outlined in Table XXII, 89 (74.2%) of the 120 patients required either no therapy or only supportive measures (such as topical ocular lubricants, cool compresses, elevation of the head of the bed to reduce orbital congestion). Six patients (5%) were treated with systemic corticosteroids; the average duration of treatment was 84 days, and the range of maximal daily dose was 40 to 80 mg of prednisone. Five patients treated with corticosteroids subsequently underwent orbital decompression, whereas optic neuropathy in one patient responded satisfactorily to the anti-inflammatory therapy. One patient required two additional, prolonged courses of prednisone after the initial corticosteroid treatment. Orbital radiotherapy was administered at another institution to treat severe orbital inflammation in one patient who moved from Olmsted County.

Twenty-four patients (20%) underwent one or more surgical procedures to treat GO, as outlined in Table XXIII. Although 22 of the 24 patients were women, the distribution by sex was not significantly different from that of the overall incident case population ($P = .3997$; two-tailed normal deviate). The average age at the time of diagnosis of ophthalmopathy was 52.5 ± 17.8 years (median, 51.6; range, 21.9 to 82.1) among this group and 42.7 ± 16.9 years (median, 41.8; range, 8.2 to 88.7) for the remaining 96 patients who did not undergo surgical intervention. The need for surgery was significantly related to age ($P < .01$; Cox proportional hazards model) but was not significantly dependent on sex ($P = .5$) or the interaction of age and sex ($P = .15$). The risk of the need for surgery was 2.6 times greater in patients older

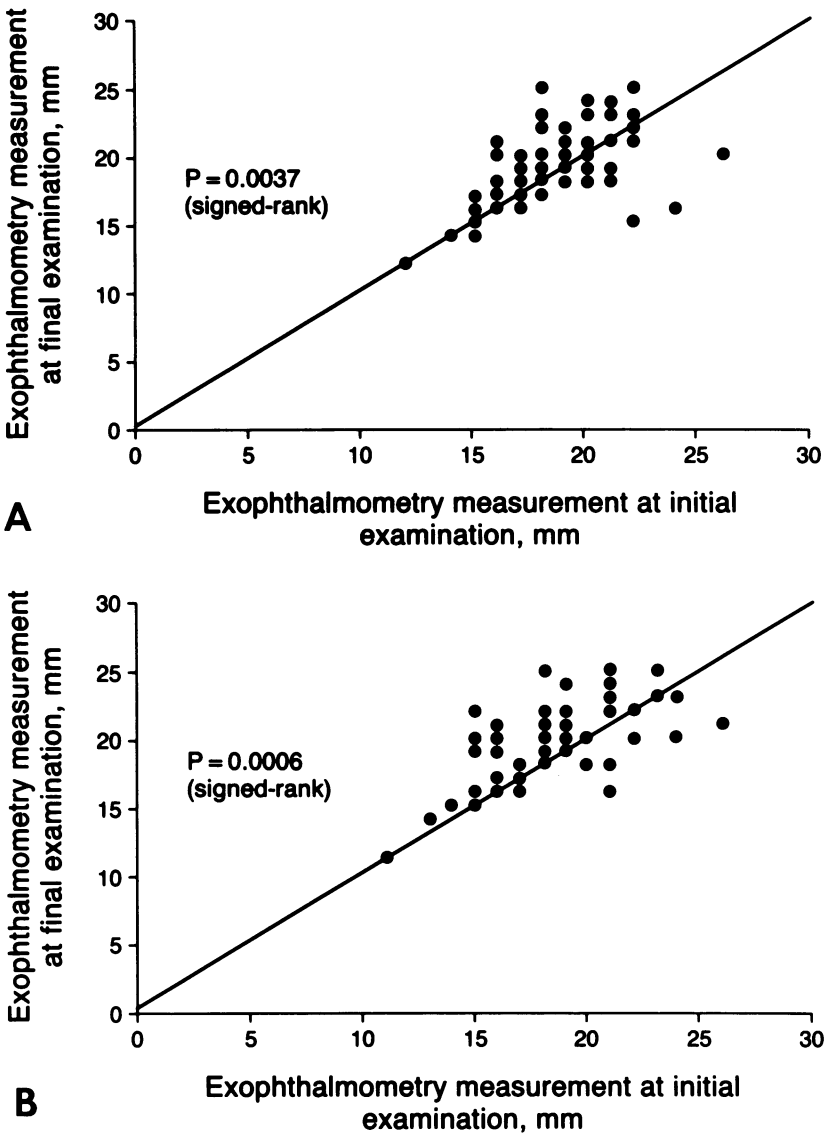

FIGURE 11

Changes in exophthalmometry measurements from initial to final examinations for incidence cohort of 120 patients with Graves' ophthalmopathy. Diagonal line is line of no change (line of identity). A, Right eye. B, Left eye.

TABLE XXII: TREATMENT OF GRAVES' OPHTHALMOPATHY AMONG 120 INCIDENT CASES

TREATMENT	NO.	%
None or supportive only	89	74.2
Systemic corticosteroids	6	5.0
No. of courses		
One (6 pt)		
Mean maximal daily dose (mg): 48.3 ± 16.0; range, 40-80		
Mean cumulative dose (mg): 2,710 ± 1,646; range, 540-5,560		
Duration of treatment (days):		
Mean, 84 ± 34		
Median, 82		
Range, 34-140		
Two (1 pt)		
Maximal daily dose: 40 mg		
Cumulative dose: 1,995 mg		
Duration of treatment: 17.7 wk		
Three (1 pt)		
Maximal daily dose: 15 mg		
Cumulative dose: 2,000 mg		
Duration of treatment: 21 wk		
Orbital radiotherapy	1	0.8
Orbital decompression	8	6.7
Strabismus surgery	11	9.2
Eyelid surgery	15	12.5

than 50 years (95% CI, 1.2 to 5.8). The cumulative probability of the need for surgery within 5 years was 23.5% in patients older than 50 years and only 12% in patients 50 years or younger (Fig 12 and Table XXIV).

The average interval between the diagnosis of GO and the initial operation was 1,187 days or 3.3 years (median, 979 days [2.7 years]; range, 6 days to 4,902 days [13.4 years]). The interval was less than 1 year for 6 patients (25%), less than 5 years for 18 patients (75%), more than 5 years for 6 patients (20.8%), and more than 10 years in 1 patient (4.2%). Twenty-two patients were in the hyperthyroid group, whereas two patients had euthyroid Graves' disease.

Ten patients underwent one operation, 7 patients had two operative sessions, 5 patients required three operations, 1 patient underwent five operations, and one patient had an extraordinarily complicated course that involved 10 surgical interventions. Nine surgeons (five ophthalmologists, three otorhinolarynogologists, and one neurosurgeon) operated on the patients with GO at our institution during the study period.

TABLE XXIII: OPHTHALMIC SURGICAL PROCEDURES AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY

CASE	SEX/AGE (YR)* AT DIAGNOSIS	DAYS FROM DIAGNOSIS TO 1ST OPERATION†	1ST OPERATION	DAYS FROM 1ST TO 2ND OPERATION	2ND OPERATION	DAYS FROM 2ND TO 3RD OPERATION	3RD OPERATION	DAYS FROM 3RD TO 4TH OPERATION	4TH OPERATION	DAYS FROM 4TH TO 5TH OPERATION
1	F/44	455	Right upper eyelid retractors recession Left upper eyelid retractors recession							
2	F/33	181	Left upper eyelid retractors recession	1292	Right upper eyelid retractors recession					
3	F/44	150	Right inferior rectus recession Left inferior rectus recession							
4‡	F/76	130	Right inferior rectus recession	42	Left superior rectus recession					
5	F/51	1908	Bilateral transantral orbital decompression§	67	Right medial rectus recession Right inferior rectus recession Left medial rectus recession Left inferior rectus recession	104	Right upper eyelid retractors recession Left upper eyelid retractors recession Right lower eyelid medial retractors recession// Left lower eyelid medial retractors recession//	52	Right inferior rectus advancement Right lower eyelid medial retractors recession//	210
6	F/49	1341	Right inferior rectus recession	203	Right inferior rectus recession Left inferior rectus recession	371	Right inferior rectus advancement			
7	F/21	502	Bilateral transantral orbital decompression§	89	Right upper eyelid retractors recession Left upper eyelid retractors recession	96	Right upper eyelid retractors recession Left upper eyelid retractors recession			
8	F/40	1784	Bilateral transantral orbital decompression¶	82	Right medial rectus recession Left medial rectus recession Left inferior rectus myotomy					

9	F/56	931	Right lower eyelid retractors recession and tarsal strip procedure# Left lower eyelid retractors recession and tarsal strip procedure#								
10	M/52	2259	Left lateral tarsorrhaphy#								
11	F/43	642	Right upper eyelid retractors recession Left upper eyelid retractors recession	93	Right upper eyelid retractors recession Left upper eyelid retractors recession						
12	F/73	6	Bilateral transantral orbital decompression§								
13	F/65	1539	Left medial rectus recession Left inferior rectus recession	44	Right upper eyelid retractors recession Left upper eyelid retractors recession	92	Right upper eyelid retractors recession	41	Left lower eyelid pentagonal block resection# Left upper eyelid retractors recession	334	
14	F/60	1027	Bilateral transantral orbital decompression§	49	Bilateral transfrontal orbital decompression§	50	Right medial rectus recession Right inferior rectus recession Left medial rectus recession				
15	F/80	2120	Right superior rectus recession Right inferior rectus recession								
16	F/82	336	Right lateral tarsorrhaphy# Right lower eyelid retractors recession	327	Right lower eyelid retractors recession Right medial tarsorrhaphy# Left upper eyelid retractors recession Left lateral tarsorrhaphy#						

TABLE XXIII: OPHTHALMIC SURGICAL PROCEDURES AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY (CONT'D)

CASE	SEX/AGE (YR)* AT DIAGNOSIS	DAYS FROM DIAGNOSIS TO 1ST OPERATION†	1ST OPERATION	DAYS FROM 1ST TO 2ND OPERATION	2ND OPERATION	DAYS FROM 2ND TO 3RD OPERATION	3RD OPERATION	DAYS FROM 3RD TO 4TH OPERATION	4TH OPERATION	DAYS FROM 4TH TO 5TH OPERATION
17	F/27	428	Bilateral transantral orbital decompression¶	38	Left medial rectus recession Left inferior rectus recession	115	Right upper eyelid retractors recession Left upper eyelid retractors recession			
18	F/59	1236	Right upper eyelid retractors recession							
19	M/69	127	Bilateral transantral orbital decompression§	270	Right medial rectus recession Left medial rectus recession					
20	F/33	4902	Left upper eyelid retractors recession							
21	F/51	1098	Right upper eyelid retractors recession Right upper eyelid blepharoplasty†† Left upper eyelid retractors recession Left upper eyelid blepharoplasty††							
22‡	F/32	2851	Left upper eyelid retractors recession							
23	F/32	560	Right upper eyelid retractors recession Left upper eyelid retractors recession Left lower eyelid retractors recession	68	Left upper eyelid levator advancement**	343	Left upper eyelid levator advancement**			
24	F/77	1964	Right medial rectus recession Right inferior rectus recession	149	Right medial rectus myotomy Right inferior rectus myotomy					

TABLE XXIII: OPHTHALMIC SURGICAL PROCEDURES AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY [SECOND HALF]

CASE	5TH OPERATION	DAYS FROM 5TH TO 6TH OPERATION	6TH OPERATION	DAYS FROM 6TH TO 7TH OPERATION	7TH OPERATION	DAYS FROM 7TH TO 8TH OPERATION	8TH OPERATION	DAYS FROM 8TH TO 9TH OPERATION	9TH OPERATION	DAYS FROM 9TH TO 10TH OPERATION	10TH OPERATION
1											
2											
3											
4											
5	Right lower eyelid medial retractors recession// Left lower eyelid medial retractors recession//										
6											
7											
8											
9											
10											
11											
12											
13	Left upper eyelid tarsonivectomy°°	1302	Right medial rectus recession Right inferior rectus recession	62	Right lower eyelid tarsal strip procedure# and blepharoplasty††	184	Bilateral transantral orbital decompression§	82	Right superior rectus recession Left superior oblique tenotomy Left medial rectus myotomy Left lateral rectus resection	112	Right lateral rectus resection Right superior rectus advancement Left lateral rectus resection

°Age at diagnosis of Graves' ophthalmopathy: mean, 52.5 ± 17.8 years; median, 51.6 years; $P < .01$ (Cox model), compared with age at diagnosis of Graves' ophthalmopathy in patients who did not undergo operation.
†Interval between diagnosis of Graves' ophthalmopathy and first operation: mean, 3.3 years; median, 2.7 years.
‡Euthyroid Graves' disease.
§To treat optic neuropathy.
//To treat medial lower eyelid entropion.
¶To treat orbital inflammation.
#To treat eyelid retraction.
°°To treat blepharoptosis.
††To treat eyelid fullness.

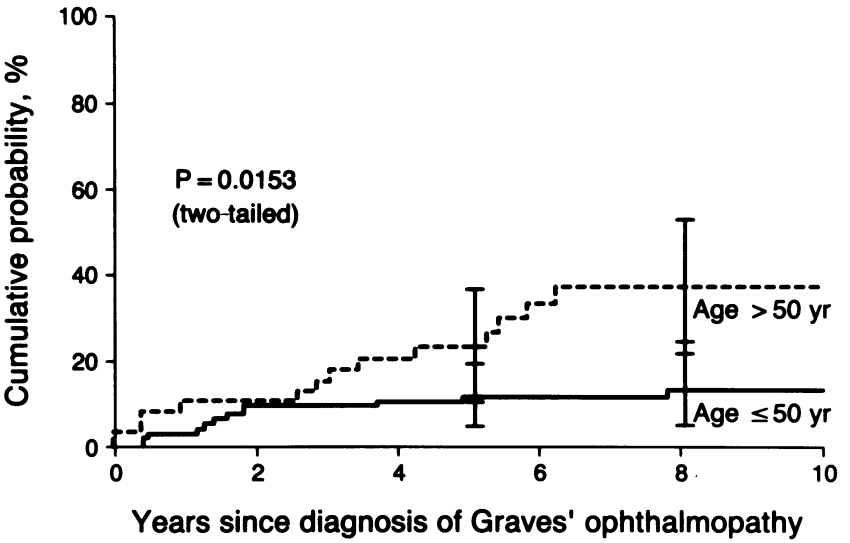

FIGURE 12
Cumulative probability (estimate with 95% confidence interval) of ophthalmic surgery for Graves' ophthalmopathy among 120 incident cases, by age at diagnosis of ophthalmopathy.

TABLE XXIV: CUMULATIVE PROBABILITY OF OPHTHALMIC SURGERY FOR GRAVES' OPHTHALMOPATHY AMONG 120 INCIDENT CASES, BY AGE AT DIAGNOSIS OF OPHTHALMOPATHY

AGE AT DIAGNOSIS OF GO (YR)	INTERVAL SINCE DIAGNOSIS OF GO (YR)	NO. OF PATIENTS STILL AT RISK	PROBABILITY ± SE (%)
≤50	1	76	2.6 ± 3.5
>50		36	9.8 ± 9.1
≤50	2	69	9.0 ± 6.4
>50		36	9.8 ± 9.1
≤50	3	67	9.0 ± 6.4
>50		32	15.0 ± 11.1
≤50	4	61	10.5 ± 6.9
>50		27	20.4 ± 12.7
≤50	5	56	12.0 ± 7.4
>50		24	23.5 ± 13.5
≤50	6	50	12.0 ± 7.4
>50		18	33.5 ± 15.8
≤50	10	36	14.0 ± 8.2
>50		11	37.2 ± 16.5

SE, standard error.

Eight patients underwent bilateral transantral orbital decompression; the operation was performed to treat optic neuropathy in six cases and to reduce severe orbital inflammatory signs and symptoms in two patients. Although optic neuropathy was bilateral in four patients and unilateral in the other two, bilateral decompressions were performed in all instances. One patient who had unilateral (right eye) optic neuropathy responded to systemic corticosteroid therapy and did not require orbital decompression. One of the patients underwent bilateral transfrontal orbital decompression after bilateral transantral orbital decompression failed to alleviate optic neuropathy. Bilateral transantral orbital decompression was the sole procedure performed in only one patient.

Strabismus operations were performed in 11 patients, 5 of whom required neither orbital nor eyelid procedures. The 11 patients underwent a total of 19 strabismus operations.

Eyelid procedures were performed in 15 patients, of whom 11 had no other types of operations. All 15 patients had operations to treat eyelid retraction (a total of 20 procedures), but 2 patients required a total of three procedures to correct blepharoptosis that resulted from eyelid retraction repair. Two patients underwent blepharoplasty to excise redundant eyelid tissue. One patient had three operations (recession of the medial portion of the lower eyelid retractors) to treat cicatricial entropion, which is a potential sequela of transantral orbital decompression.

The cumulative probabilities of undergoing ophthalmic surgery of any type to treat GO are illustrated in Fig 13 and outlined in Table XXV. The probability of operative intervention was 5% by 1 year after the diagnosis of ophthalmopathy, 9.3% after 2 years, 15.9% after 5 years, and 21.8% after 10 years.

The cumulative probabilities for orbital decompression, strabismus surgery, or eyelid procedures are depicted in Figs 14 through 16 and Tables XXVI through XXVIII, respectively. The chance of requiring orbital decompression was 1.7% by 1 year after diagnosis of GO, 5.3% by 5 years, and 8% at 10 years. The cumulative probability of having undergone extraocular muscle surgery for strabismus was 1.7% at 1 year, 6.2% at 5 years, and 10.6% by 6 years after the diagnosis of ophthalmopathy and thereafter. The probabilities of operative intervention to correct eyelid malpositions and abnormalities at 1, 5, and 10 years after the diagnosis of GO were 1.7%, 9.7%, and 13.4%, respectively.

The cumulative probability of undergoing any type of ophthalmic surgical procedure to treat GO was analyzed by age, comparing incident case patients 50 years of age or younger with those who were older than 50 years (Fig 12 and Table XXIV). The difference between the two groups was significant ($P = .0153$; two-tailed log-rank test).

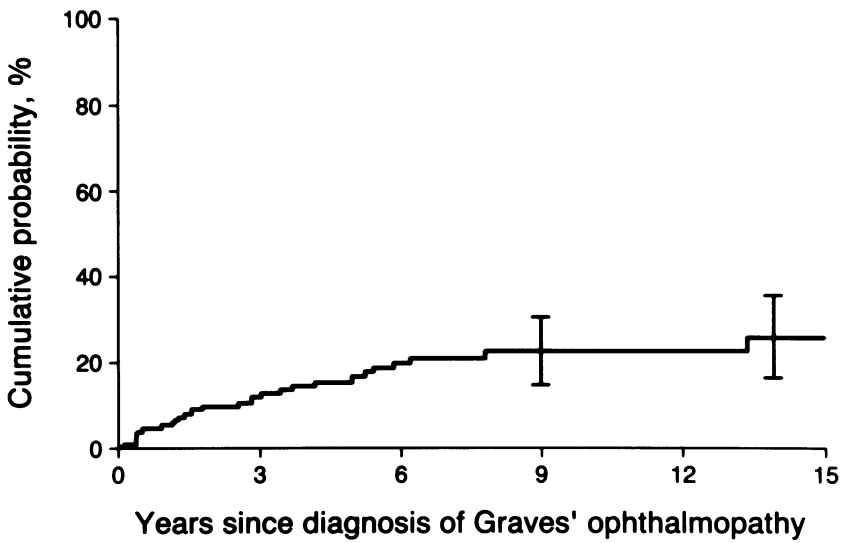

FIGURE 13
Cumulative probability (estimate with 95% confidence interval) of ophthalmic surgery for Graves' ophthalmopathy among 120 incident cases.

TABLE XXV: CUMULATIVE PROBABILITY OF OPHTHALMIC SURGERY FOR GRAVES' OPHTHALMOPATHY AMONG 120 INCIDENT CASES

TIME SINCE DIAGNOSIS OF GO (YR)	NO. OF PATIENTS STILL AT RISK	PROBABILITY ± SE (%)
1	112	5.0 ± 3.9
2	105	9.3 ± 5.2
3	99	11.1 ± 5.7
4	88	13.9 ± 6.3
5	80	15.9 ± 6.8
6	68	19.2 ± 7.5
10	47	21.8 ± 8.0

SE, standard error.

The relationship between smoking and the need for ophthalmic surgery was analyzed with the log-rank test. There were no significant differences between smokers and nonsmokers in the cumulative probabilities of undergoing surgery of any type (P = .7251) or specifically for orbital decompression (P = .1772), strabismus operations (P = .3544), or eyelid surgery (P = .6479).

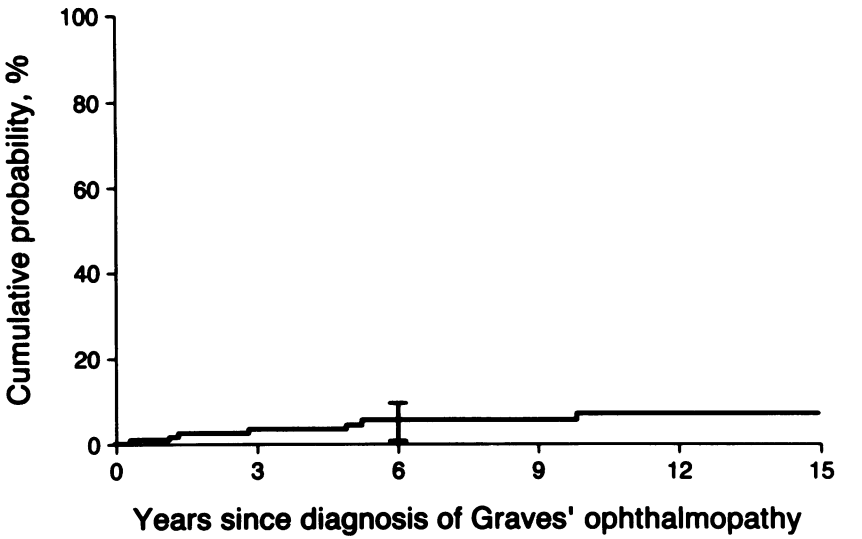

FIGURE 14
Cumulative probability (estimate with 95% confidence interval) of orbital decompression among 120 incident cases of Graves' ophthalmopathy.

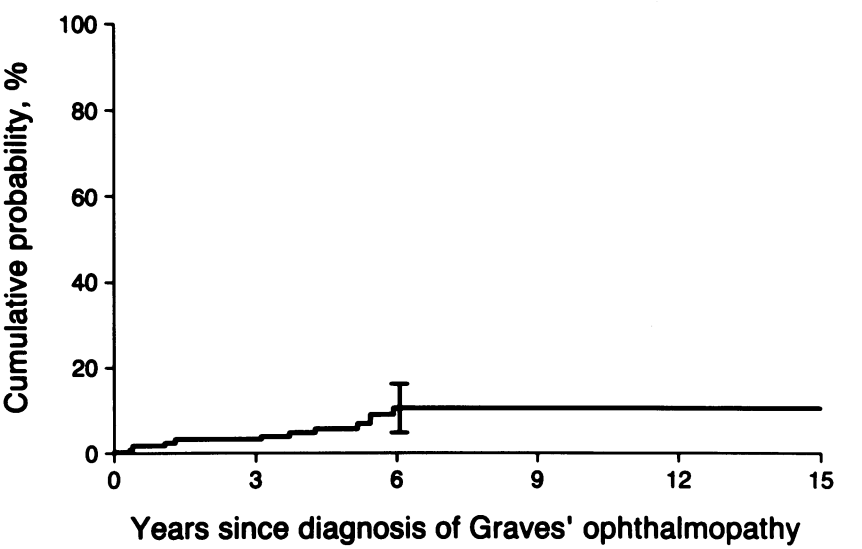

FIGURE 15
Cumulative probability (estimate with 95% confidence interval) of strabismus surgery among 120 incident cases of Graves' ophthalmopathy.

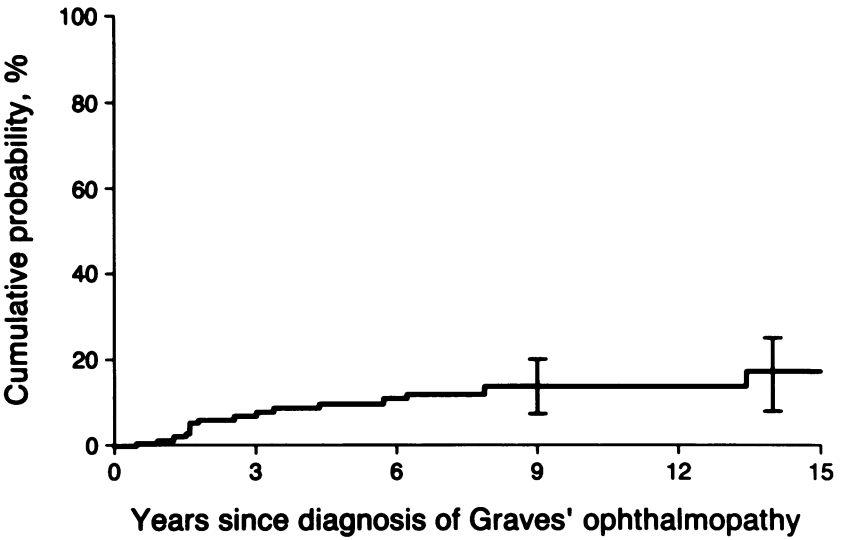

FIGURE 16
Cumulative probability (estimate with 95% confidence interval) of eyelid surgery among 120 incident cases of Graves' ophthalmopathy.

TABLE XXVI: CUMULATIVE PROBABILITY OF ORBITAL DECOMPRESSION AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY

TIME SINCE DIAGNOSIS OF GO (YR)	NO. OF PATIENTS STILL AT RISK	PROBABILITY ± SE (%)
1	116	1.7 ± 2.3
2	112	3.4 ± 3.2
3	107	4.3 ± 3.7
4	99	4.3 ± 3.7
5	91	5.3 ± 4.1
6	79	6.3 ± 4.6
10	55	8.0 ± 5.5

SE, standard error.

TABLE XXVII: CUMULATIVE PROBABILITY OF STRABISMUS SURGERY AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY

TIME SINCE DIAGNOSIS OF GO (YR)	NO. OF PATIENTS STILL AT RISK	PROBABILITY ± SE (%)
1	116	1.7 ± 2.3
2	112	3.4 ± 3.3
3	108	3.4 ± 3.3
4	98	5.2 ± 4.1
5	90	6.2 ± 4.5
6	76	10.6 ± 6.0
10	53	10.6 ± 6.0

SE, standard error.

TABLE XXVIII: CUMULATIVE PROBABILITY OF EYELID SURGERY AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY

TIME SINCE DIAGNOSIS OF GO (YR)	NO. OF PATIENTS STILL AT RISK	PROBABILITY ± SE (%)
1	116	1.7 ± 2.3
2	109	6.0 ± 4.3
3	104	6.8 ± 4.6
4	94	8.7 ± 5.1
5	86	9.7 ± 5.5
6	75	10.8 ± 5.8
10	51	13.4 ± 6.7

SE, standard error.

FOLLOW-UP

The distribution of the number of ophthalmic examinations is outlined in Table XXIX. Twenty-one patients (17.5%) were not examined by an ophthalmologist subsequent to the initial visit (but follow-up information was obtained from the mail and telephone survey, as described below). The mean and median intervals between the initial and final ophthalmic examinations were 1,740 days (4.8 years) and 1,313 days (3.6 years), respectively. Thirty-seven (30.8%) of the 120 incident case patients had follow-up of less than 1 year. In contrast, 46 patients (38.3%) were examined 5 years or more after the initial diagnosis of GO and 22 patients (18.3%) had 10 years or more of ophthalmic follow-up. The average and median ages of patients at the time of the final ophthalmic examination were 51.1 ± 18.3 years and 48.3 years, respectively (range, 11.6 to 90.4 years).

TABLE XXIX: NO. OF OPHTHALMIC EXAMINATIONS AMONG 120 INCIDENT CASES OF GRAVES' OPHTHALMOPATHY

NO. OF EXAMINATIONS	NO. OF PATIENTS	%
1	21	17.5
2	33	27.5
3	26	21.7
4	15	12.5
5	12	10.0
6	3	2.5
7	2	1.7
8	2	1.7
9	3	2.5
10	1	0.8
12	1	0.8
14	1	0.8

Interval from initial to final ophthalmic examinations:
Mean, 4.8 yr
Median, 3.6 yr
Range, 0-15.6 yr
<1 yr: 37 pt (30.8%)
>5 yr: 46 pt (38.3%)
>10 yr: 22 pt (18.3%)
Age at final ophthalmic examination (99 patients)
Mean, 51.1 ± 18.3 yr
Median, 48.3 yr
Range, 11.6-90.4 yr

In addition to the chart review, long-term follow-up was achieved in 92 (76.7%) of the 120 incident cases by completion of either the mail questionnaire or a telephone interview by a member of the Mayo Clinic Survey Research Center (Table XXX). Seventeen patients (14.2%) declined to participate in the follow-up survey and 11 patients (9.2%) had died.

The mean and median intervals between the initial ophthalmic examination and most recent follow-up (the final examination, the completion of the follow-up survey, or telephone follow-up) were 3,445 days (9.4 years) and 3,576 days (9.8 years), respectively. The range of follow-up varied from 64 days to 6,353 days (17.4 years). Follow-up was less than 1 year for two (1.7%) patients (64 days and 197 days). Follow-up of more than 5 years was available for 96 patients (80%), whereas follow-up exceeding 10 years was achieved for 59 patients (49.2%).

Nearly one half of the survey respondents reported deterioration of their vision in the interval since their last ophthalmic examination at our institution. In 58.5% of cases the underlying cause was known; cataract and refractive changes were the most frequent causes, and in no case was

TABLE XXX: RESPONSES TO FOLLOW-UP QUESTIONNAIRE: PATIENT SELF-ASSESSMENT

No. of respondents: 92 (76.7% of 120 incident cases)
No. deceased: 11 (9.2% of 120 incident cases)
No. declined: 17 (14.2% of 120 incident cases)

Interval from initial examination to most recent follow-up:
- Mean, 3,445 days (9.4 yr)
- Median, 3.576 days (9.8 yr)
- Range, 64-6,353 days (17.4 yr)
  - <1 yr: 2 pt (1.7%)
  - >5 yr: 96 pt (80%)
  - >10 yr: 59 pt (49.2%)

Have you had any deterioration of the sharpness of your vision since your last eye examination? (89 respondents)
- No: 48 (53.9%)
- Yes: 41 (46.1%)
  - If yes, is the cause known?
    - No: 17 (41.5%)
    - Yes: 24 (58.5%)
      - Cataract: 6 (25% of 24 respondents; 6.7% of 89 respondents)
      - Presbyopia: 6 (25% of 24 respondents; 6.7% of 89 respondents)
      - Refractive error change (correctable): 4 (16.7% of 24 respondents; 4.5% of 89 respondents)
      - Macular degeneration: 3 (12.5% of 24 respondents; 3.4% of 89 respondents)
      - Keratoconjunctivitis sicca: 3 (12.5% of 24 respondents; 3.4% of 89 respondents)
      - Glaucoma: 1 (4.2% of 24 respondents; 1.1% of 89 respondents)
      - Amoebic keratitis: 1 (4.2% of 24 respondents; 1.1% of 89 respondents)

Have you had double vision in the past 4 weeks? (90 respondents)
- No: 81 (90%)
- Yes: 9 (10%)
  - If yes, was the double vision intermittent or constant?
    - Intermittent: 7 (77.8% of 9 respondents; 7.8% of 90 respondents)
    - Constant: 2 (22.2% of 9 respondents; 2.2% of 90 respondents)
  - If constant, is the double vision correctable with glasses?
    - No: 0
    - Yes: 2

Have your eyes felt uncomfortable in the past 4 weeks? (89 respondents)
- No: 60 (67.4%)
- Yes: 219 (32.6%)
  - If yes, what is the cause of the discomfort?
    - Dry eyes: 21 (72.4% of 29 respondents; 23.6% of 89 respondents)
    - Allergy: 2 (6.9% of 29 respondents; 2.2% of 89 respondents)
    - Upper respiratory tract infection: 1 (3.4% of 29 respondents; 1.1% of 89 respondents)
    - Migraine headache: 1 (3.4% of 29 respondents; 1.1% of 89 respondents)
    - "Pressure behind eyes": 1 (3.4% of 29 respondents; 1.1% of 89 respondents)
    - Unknown: 3 (10.3% of 29 respondents; 3.4% of 89 respondents)

Have you had any treatment for eye problems since your last examination? (92 respondents)
- No: 91 (98.9%)
- Yes: 1 (1.1%)
  - If yes, what type of treatment did you have?
    - Orbital radiotherapy: 1 (1.1%)

TABLE XXX: RESPONSES TO FOLLOW-UP QUESTIONNAIRE: PATIENT SELF-ASSESSMENT

Has the appearance of your eyes returned to what it was prior to development of thyroid disease? (86 respondents)
No: 52 (60.5%)
Yes: 33 (38.4%)
Undecided: 1 (1.2%)
Do your eyes now appear normal? (91 respondents)
No: 47 (51.6%)
Yes: 42 (46.2%)
Undecided: 2 (2.2%)
Are you satisfied with the appearance of your eyes? (87 respondents)
No: 33 (37.9%)
Yes: 53 (60.9%)
Undecided: 1 (1.1%)

decreased vision attributed to GO. Nine patients (10% of respondents) had experienced diplopia within the previous 4 weeks. In seven instances the double vision was intermittent, and for two persons it was constant. Both of these persons, however, achieved single vision with spectacle correction. Nearly one third of respondents described ocular discomfort during the preceding 4 weeks; the most frequent cause, in 72% of patients, was dry eyes. Only 1 (1.1%) of 92 respondents had had any treatment for eye problems since the last examination at our institution; this patient had undergone orbital radiotherapy for orbital congestion after moving from Olmsted County. Regarding patients' assessment of the appearance of their eyes, 60.5% of the respondents believed that their appearance had not returned to what it had been prior to the development of thyroid disease, 51.6% felt that their eyes appeared abnormal, and 37.9% were dissatisfied with the appearance of their eyes.

DISCUSSION

Observations or comments regarding the epidemiology of GO have appeared in several published studies, none of which, however, were population-based. The earliest reports, in which consecutive patients were studied and "an attempt [was] made to trace the natural history of exophthalmos, ophthalmoplegia and related signs of Graves' disease," were authored in the 1940s by Rundle[92] and Rundle and Wilson.[93] Fifteen-year follow-up data were published by Hales and Rundle[94] in 1960.

Two studies of patients examined at the Mayo Clinic were conducted during the next decade. In 1967, Hamilton and colleagues[15] compared information on patients who had GO and Graves' disease in the overall

patient population at that institution in 1946 and 1947 (when thyroidectomy was the primary treatment for hyperthyroidism) with data from patients examined in 1963 and 1964 (when radioiodine was the preferred therapy for thyrotoxicosis). This study is the source of the often-cited statistic relating the prevalence of severe ophthalmopathy among all patients with hyperthyroidism to be 3% to 5%.[23,74,95-98] A second Mayo Clinic review of thyroid disease was published in 1970 by Furszyfer and colleagues,[99] but eye changes were not addressed.

Tunbridge and coauthors,[100] in 1977, reported epidemiologic data from patients with thyroid disease in Whickham, County Durham, United Kingdom; in that study, however, and in others that were recently summarized by Berglund and coworkers,[101] the incidence and prevalence of ophthalmopathy were not determined. Excellent recent reports describing both thyroid dysfunction and ophthalmopathy have been published by Wiersinga and associates,[31,102-104] by Kendler and colleagues,[36] and by Perros and coworkers,[37] but the subjects studied were consecutive referred patients.

The focus of the current project was to provide new information by describing the epidemiologic characteristics and clinical courses of patients with autoimmune thyroid disease in a population-based setting. Comments on selected facets of the data that were collected are outlined below.

EPIDEMIOLOGIC CHARACTERISTICS

Demographics

Women and girls composed 86% of the incident cases of GO in this study, confirming the female preponderance in nearly all reports of this disorder. Mulvaney, in contrast, believed that the "thyrotrophic" form of exophthalmos was three to four times more likely to affect men than women,[54] whereas the "thyrotoxic" subtype was more prevalent in women by approximately the same ratio.[55] Compared with overall populations of patients with Graves' disease (for example, the Whickham survey by Tunbridge and colleagues,[100] in which the male-female ratio was 0.10), there has been a higher proportion of men among patients with ophthalmopathy (0.26,[103] 0.30,[36] and 0.32[65]). In some studies that reviewed the results of treatment, the ratio of men has been even greater (0.4[105] and 1.0[106]); this finding has been interpreted as reflecting a bias that men more frequently may have severe disease that requires therapy.[36,107] In the current study, however, the need for surgical intervention was not significantly different between men and women.

The age-adjusted incidence rates for females and males were 16 cases and 3 cases, respectively, per 100,000 population per year, and there was no

evidence that the incidence rates increased or decreased significantly during the 15-year interval studied (Figs 5 and 6). Peak incidence rates were noted for women between ages 40 and 44 years and 60 and 64 years and for men between ages 45 and 49 years and 65 and 69 years. No physiologic causes for this bimodal pattern were apparent, although it is possible that the slight lag in diagnosis among men may reflect a tendency to seek medical attention later in the clinical course. Brain,[108] in 1959, studied 100 consecutive patients (68 females and 32 males, ranging in age from 13 to 80 years) with "exophthalmic exophthalmoplegia" and determined that the maximal incidence for females was in the fifth decade, whereas nearly half of the cases among males occurred in the sixth decade.

All of the patients in this review were white, reflecting the racial distribution of Olmsted County (96% white).

Chronology

Gorman[109] emphasized the close temporal relationship between the onsets of GO and hyperthyroidism in a study of patients who were scheduled for orbital decompression. A figure (Fig 17), which compares the onset of eye symptoms to the time of diagnosis of hyperthyroidism, from that report is frequently cited to illustrate this association. Eighty-one percent of the patients studied by Gorman developed eye symptoms within 18 months before or 18 months after the diagnosis of thyrotoxicosis. A recent updated

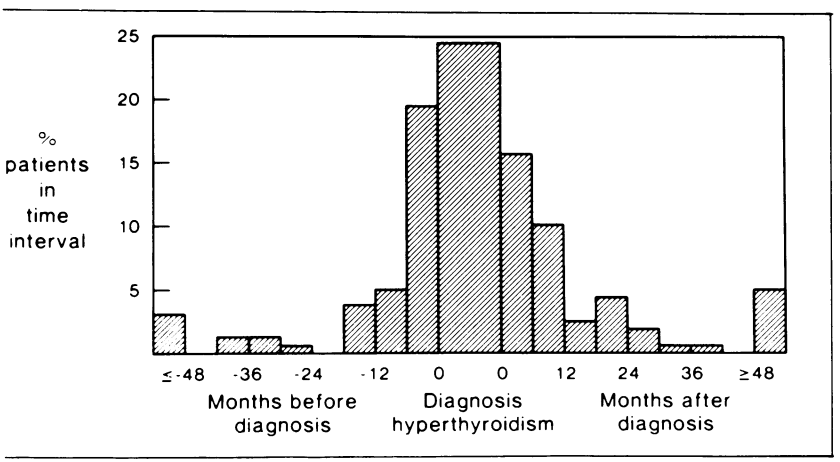

FIGURE 17

Onset of eye symptoms in relationship to time of diagnosis of hyperthyroidism (zero on horizontal axis). Number of patients who first experienced eye symptoms within a given 6-month period is expressed as percentage of entire group. (From Gorman.[109] By permission of Mayo Foundation.)

report[98] with additional patients from the same institution noted that 258 of 371 patients (69.5%) with hyperthyroidism had the onset of eye symptoms within 1 year before or 1 year after the diagnosis of thyroid dysfunction; with an increase in the range to 2 years before or after diagnosis, 316 of the 371 patients (85.2%) were included. In the current study, 69.5% (48 of 69) of patients with hyperthyroidism who had ocular symptoms initially noted their symptoms within 18 months before or 18 months after the thyroid diagnosis (Fig 18). The slightly higher frequency of patients in Gorman's original study[109] who had eye symptoms at the time of thyroid diagnosis perhaps may be explained by the population in that study, that is, patients scheduled for orbital decompression, who might be expected to have more severe ophthalmopathy than the incidence cohort of the current report.

The relationship of the diagnosis of GO to the diagnosis of hyperthyroidism is depicted in Fig 19. Twenty-two of 108 patients (20.3%) had simultaneous diagnoses, and in 66 (61.1%) ophthalmopathy developed within 1 year of the onset of thyrotoxicosis. Such a close temporal association has been cited by several investigators as evidence that ophthalmopathy is etiologically related to thyroid dysfunction.[31,65,110,111]

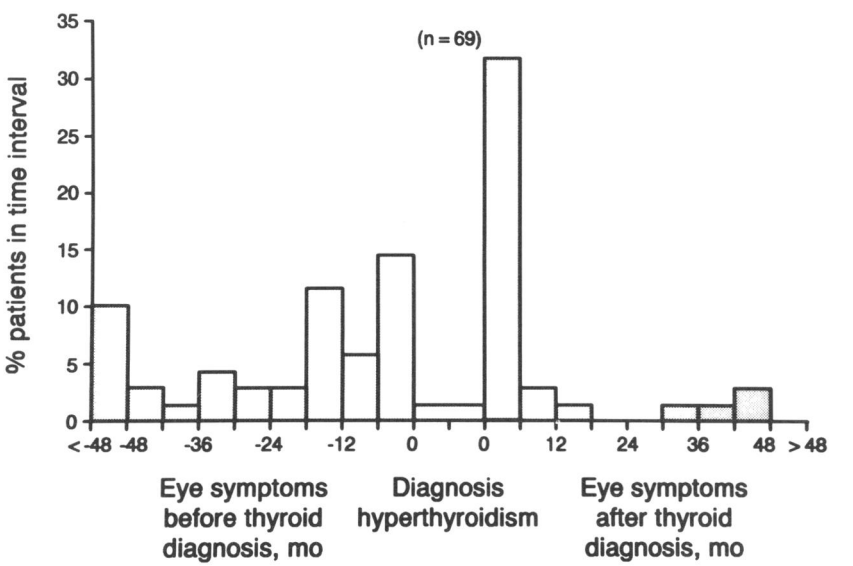

FIGURE 18
Onset of eye symptoms in relationship to time of diagnosis of hyperthyroidism among 69 patients (zero on horizontal axis). Number of patients who first experienced eye symptoms within a given 6-month period is expressed as percentage of entire group.

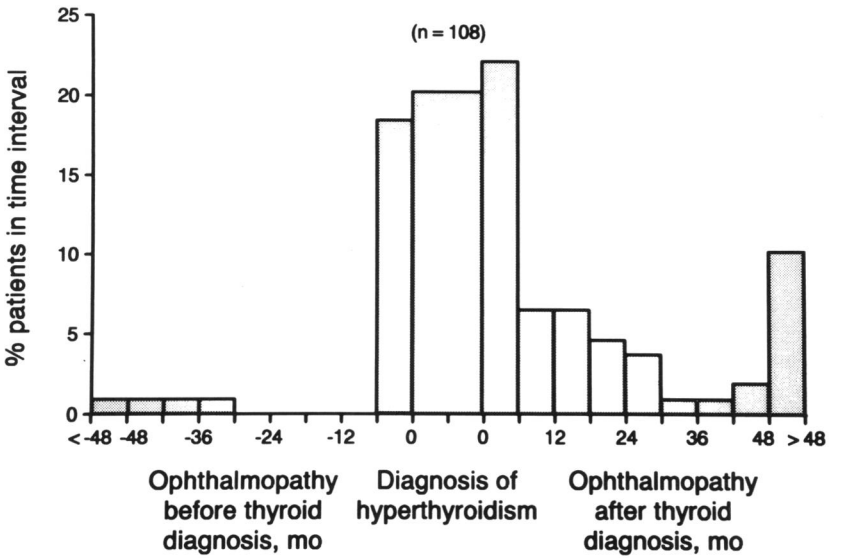

FIGURE 19
Diagnosis of Graves' ophthalmopathy in relationship to time of diagnosis of hyperthyroidism (zero on horizontal axis). Number of patients is expressed as percentage of entire group.

Among the more interesting patients in the incidence cohort were two girls in whom thyroid dysfunction and ophthalmopathy developed before the age of 10 years. In both instances the presenting sign was prominence of the left eye. In the younger of the two patients, the initial ophthalmic examination was performed at age 8.2 years, 7 months after subjective proptosis of the left eye had been noted by the parents. Exophthalmometry measurements were 15 and 17 mm for the right and left eyes, respectively. Computed tomography demonstrated enlargement of the medial rectus muscle in each orbit. The patient had no thyroid symptoms, but the serum total thyroxine and thyroid-stimulating immunoglobulin values were slightly increased. No treatment for either the thyroid or the ophthalmic findings was necessary, and subsequent examinations 1 year and 4 years after diagnosis demonstrated normal ocular function, symmetric exophthalmometry measurements, and normal results of thyroid function studies.

The second patient had been examined in the ophthalmology department at the Mayo Clinic at the age of 4 years, at which time no abnormalities were noted. At age 9.1 years, she returned with an 11-week history of proptosis of the left eye. There were no ocular symptoms, and the uncorrected visual acuity was 20/20 for each eye. Krahn exophthalmometry measurements

were 17 mm and 21 mm for the right and left eyes, respectively; there was left upper eyelid retraction of 2 mm (with eyelid fissures of 8 and 10 mm for the right and left eyes, respectively), and mild resistance to retropulsion of the left globe was noted. The patient had symptoms of hyperthyroidism, and a physical examination disclosed a diffuse goiter, total thyroxine value of 16.3 μg/dl, free thyroxine level of 4.1 ng/dl, and triiodothyronine value of 382 ng/dl. The family history was positive for Graves' disease. The patient was treated with propylthiouracil for 25 months and then subsequently underwent a subtotal thyroidectomy 4½ years after the diagnosis of hyperthyroidism. She was asymptomatic at her most recent ophthalmic examination, 10 years after diagnosis, and no abnormalities were identified. Exophthalmometry demonstrated regression in the proptosis of the left eye, with measurements of 19 and 18 mm for the right and left eyes, respectively.

CLINICAL CHARACTERISTICS AND COURSE

Thyroid Status and Treatment

Classification of Thyroid Dysfunction: As expected, hyperthyroidism was the predominant type of thyroid dysfunction, occurring in 90% of patients, among the incident cases studied. Hashimoto's thyroiditis was diagnosed in 4 (3.3%) of the 120 patients in the cohort; although Solomon and colleagues[22] stated that the association is rare, Bahn and Gorman[49] indicated that as many as 10% of patients with GO have Hashimoto's thyroiditis. The latter estimate is probably more accurate; the frequency of diagnosis of Hashimoto's thyroiditis would almost certainly be greater if the serum of every patient with ophthalmopathy were checked for the presence of cytotoxic or thyroid-blocking antibodies or if the thyroid gland were examined histopathologically for lymphocytic infiltration. Most published reports linking the two entities describe only individual cases or a few patients.[15,112-118] Primary hypothyroidism likewise is infrequently associated with GO,[119-128] and the current study includes only one patient (0.8%).

Seven patients (5.8%) among the incidence cohort of 120 patients never manifested clinical or laboratory evidence for thyroid dysfunction during their clinical course and were thereby classified as having euthyroid Graves' disease. This peculiar entity has been described by many investigators,[21-23, 38,39,41,53-55,60,65,92,94,102,105,108,109,120,121,125,129-148] but the reports by Rundle and Wilson,[129] Hall and coworkers,[21] and Solomon and colleagues[22] were the most important in its definition. Jakobiec and Henkind,[141] in an editorial published in 1981, noted that approximately one fifth of patients with GO have no detectable abnormalities of thyroid dysfunction at the time that the eye changes are diagnosed, but that laboratory testing later in the

clinical course may identify evidence for thyroid disease. The widespread availability of sensitive investigative tools to discover subtle abnormalities of thyroid function or control may allow the identification of some thyroid irregularity in virtually all patients with euthyroid Graves' disease.[65] Further advances and refinements in laboratory medicine most likely will either diminish or eliminate this classification subgroup of GO.

The Relationship of Graves' Ophthalmopathy to the Treatment of Hyperthyroidism: The possible effect on ophthalmopathy of treating hyperthyroidism with medications, radioactive iodine, or thyroidectomy has been debated for many years. The medical,[149-154] radioablative,[155-157] and surgical[108,155,156,158-164] options each have had their proponents, whereas other investigators[15,33,93,109,110,143,165-170] have suggested that no method is clearly superior to or worse than the others. Radioiodine, in particular, has been suspected as exacerbating ophthalmopathy,[43,154,162,171-176] particularly if hypothyroidism is induced but not treated promptly.[177,178]

Endocrinologists at our institution have favored thyroid ablation with radioactive iodine as the preferred treatment of hyperthyroidism. An assessment of changes in ophthalmic status was formulated for 71 of the 97 patients in the current study who were treated with ^{131}I. Signs and symptoms improved after treatment in 28% of patients, worsened in 25%, and were unchanged in 47%; the time courses of changes in patients who apparently improved or worsened were nonspecific. Although a definitive answer regarding the possible effect of antithyroid therapy on ophthalmopathy is not provided by this retrospective study, the avoidance of posttreatment hypothyroidism and the early achievement of euthyroidism seem prudent.[17,49,154,179,180]

General Medical History and Physical Findings

Irradiation of the Neck for Nonthyroidal Neoplasms: Thyroid disease, in some instances accompanied by ophthalmopathy, has been reported to develop in patients who have been treated with radiation to the neck for nasopharyngeal carcinoma, breast carcinoma, laryngeal carcinoma, or, particularly, Hodgkin's disease.[95,181-189] One patient in the current study received radiation therapy to the neck for laryngeal cancer, but the treatment was administered 15 years after Graves' hyperthyroidism had been diagnosed, and it seemed to have no effect on the ocular status.

Smoking: Hägg and Asplund[190] were the first investigators to publish the suggestion that a relationship exists between smoking and the development of "severe endocrine ophthalmopathy." Bartalena and coworkers[191] determined that the percentage of smokers among women with GO was 64% and that the percentage of heavy smokers was higher among patients with more

severe ophthalmopathy; however, they concluded that it is "unlikely that smoking [is] responsible for the autoimmune phenomena related to Graves' disease and ophthalmopathy" because Hashimoto's thyroiditis (which they regarded as "the typical organ-specific thyroid autoimmune disease") was not associated with a higher prevalence of smokers in their study. Shine and colleagues[192,193] found that approximately two thirds of patients with severe GO were smokers, a significantly higher percentage than smokers in the general population of the United Kingdom or patients with Graves' disease but without eye changes; the investigators believed that smoking may be a contributing factor in the development of GO, possibly by disrupting T-cell function or altering the patient's immune system in some other way. Balazs and colleagues[194] responded to the opinions of Shine and associates by stating that smoking is unlikely to affect the immune system, and they proposed a potential role for genetic factors (specifically, HLA-DR3, HLA-B8, or both). Tellez and coworkers[195] studied the smoking habits of patients at an endocrine clinic in England and concluded both that tobacco use is related to ophthalmopathy and that persons of European ancestry are more than six times more likely than persons of Asian heritage to develop thyroid eye disease. Nunery and coauthors[79] identified a higher percentage of smokers among older patients with ophthalmopathy and in persons whose ophthalmic abnormalities were more severe.

Two case-control studies that evaluated the relationship between smoking and GO were published in 1993. Prummel and Wiersinga[35] determined that the risk of developing GO was increased nearly eight times by smoking, and they also found that Graves' disease was more likely to occur among smokers (odds ratio, 1.9). The authors identified smoking as one of several possible factors that may induce Graves' disease and ophthalmopathy in genetically predisposed persons. Winsa and coworkers[196] also concluded that smoking is a risk factor for Graves' disease, but they believed that tobacco use is not strongly associated with ophthalmopathy at the time of diagnosis. Persistent smoking, however, was thought to enhance, by unknown mechanisms, the severity of eye disease in patients who develop ophthalmopathy during the course of treatment for hyperthyroidism.

The frequency of smokers in the current study is remarkably similar to that determined by Bartalena and colleagues[191] and by Shine and coworkers.[192,193] Information on smoking habits among incident patients with GO was compared with pertinent unpublished data from the Rochester Blood Pressure Study, a survey of persons who were 35 years of age or older in 1986. Comparisons of "current smokers" could not be made because the definition in the blood pressure study specified that subjects smoked 10 cigarettes daily, whereas the GO project did not require a minimal number

for designation as a smoker. Additionally, the number of men among the incident cases of ophthalmopathy was too small to permit meaningful comparisons. Therefore, comparisons were made between women with GO who were 35 years of age or older and who had ever smoked cigarettes and appropriate patients from the Rochester Blood Pressure Study. There were more smokers among patients with ophthalmopathy than in the community survey in all age-groups (35 to 44 years, 82% versus 38%; 45 to 54 years, 60% versus 38%; 55 to 64 years, 41% versus 38%; and 65 to 74 years, 33% versus 32%), except for women older than 75 years (0% versus 14%). The only difference that was statistically significant, however, was among women between ages 35 and 44 years ($P = .00007$, χ^2 test; $P = .00014$, Fisher's exact test). This interval overlaps, in part, one of the two rates of peak incidence of GO in women (ages 40 to 44 years).

Although the exact mechanism by which smoking apparently increases the risk of developing GO is unknown, an etiologic association seems likely. Some investigators, noting that the inferior and medial rectus muscles are the extraocular muscles most likely to be enlarged in GO, have suggested informally that cigarette smoke may enter the maxillary and ethmoid sinuses and exert a toxic effect that causes pathologic changes in the inferomedial tissues of the neighboring orbits.

Pregnancy: Nüssgens and coworkers[197] recently described a 24-year-old white woman in whom GO worsened markedly during pregnancy. Exophthalmometry measurements increased to 28 mm and visual acuity decreased to 20/200 for each eye. Glucocorticoids were prescribed, but the patient's condition deteriorated after delivery. Radiotherapy was instituted, and there was gradual improvement to near normal for both proptosis and vision. This case was presented as the most severe reported example of ophthalmopathy associated with pregnancy.

Among the incident cases studied in this investigation, ophthalmopathy developed during pregnancy in three patients and within the first 6 months after delivery in an additional two patients. The epidemiologic and clinical characteristics of these six patients did not differ from those of the remainder of the incidence cohort.

Stress: The role of stress as a contributory factor in the development of Graves' disease has been thoroughly reviewed,[198-200] but the issue is difficult to settle because "the main stumbling block is the difficulty in defining, much less quantifying, 'stress' in objective terms on which scientists can agree."[201] A major stressful life event, such as the death of a spouse or close family member, divorce, or loss of a job, was identified by review of the medical record in less than 5% of the incident cases, which almost certainly underestimates the true frequency. A prospective biopsychosocial study

would be more appropriate to determine whether stress is significantly associated with thyroid dysfunction, ophthalmopathy, or both.[201]

Thyroid Dermopathy and Thyroid Acropachy: Pretibial myxedema and clubbing of the digits are uncommon extrathyroidal manifestations of autoimmune thyroid disease. Thyroid dermopathy rarely occurs without coexistent ophthalmopathy[41,202-204] and has been considered a possible marker for more severe disease. A recent report by Fatourechi and associates,[205] however, found no difference in the clinical characteristics and response to transantral decompression in patients with pretibial myxedema and those who did not have dermopathy.

Acropachy consists of clubbing of the fingers and toes, subperiosteal new bone formation (which is radiographically distinct from pulmonary osteoarthropathy) in the phalanges and distal long bones, and swelling over the extremities. Its association with thyroid dysfunction was originally noted by Thomas in 1933[206] and subsequently has been described by several investigators.[112,203,204,207-211] Acropachy is considered to be even more unusual than thyroid dermopathy and allegedly is not found without concomitant eye and skin changes.

Pretibial myxedema and thyroid acropachy were present in 4% and 1%, respectively, of the incident cases in the current study. The severity of ophthalmopathy was not worse among these patients, none of whom had optic neuropathy or underwent orbital decompression.

Concomitant Systemic Diseases: No significant associations between GO and concomitant systemic disorders were found (Table XII). Diabetes mellitus occurred in only 2 of the 120 incident cases, which may appear to be fewer than expected. Prevalence rates of diabetes mellitus in Rochester, Minnesota, were determined by Melton and associates[212]; from this information it can be calculated that 2.71 cases of diabetes mellitus would be expected among the 120 patients we studied, which is similar to the frequency that was documented.

The association of myasthenia gravis with hyperthyroidism, GO, or both has been recognized for many years.[53,55,213-221] Although approximately 5% of patients with myasthenia gravis have Graves' disease, only 1% or less of patients with thyroid dysfunction have concomitant myasthenia.[216,221] This result is consistent with the finding of 1 patient (0.8%) with myasthenia among the 120 incident cases of GO in this study. Incidence or prevalence rates for myasthenia gravis among the Olmsted County population have not been calculated.

Brain[108] noted the presence of several miscellaneous conditions, including persistent lactation and gynecomastia, lipodystrophy, and generalized edema, in patients with GO, and Furszyfer and colleagues[99] found a correla-

tion between pernicious anemia and Graves' disease. No such associations were noted among the patients studied in the current report.

Clinical Features of Graves' Ophthalmopathy

Eyelid Retraction: The preeminence of eyelid retraction as a characteristic feature of dysthyroid ophthalmopathy has been known since at least 1869, when Stellwag[222] wrote that the sign was almost pathognomonic for Basedow's disease. Pochin,[223] in the late 30s, may have been the first author to describe unilateral retraction in association with Graves' disease. Although the eyelid malposition may improve as thyrotoxicosis is treated,[224] in a sizable minority of patients, and in those who do not have hyperthyroidism, eyelid retraction may persist in as many as 40% of affected patients for many years,[94] presumably from scarring between the inflamed eyelid retractors and the surrounding orbital tissues.[225,226] Of interest, however, is a recent study of 10,809 patients with Graves' disease who had been rendered euthyroid, in which only 21 patients (0.2%) reportedly had persistent upper eyelid retraction.[227]

Eyelid retraction was the most common sign of GO in this incidence study, being present at diagnosis in 75% of patients and occurring at some point in the clinical course in 90% of individuals. Nearly one half (45%) of the patients had eyelid retraction at the most recent examination; the difference in frequency between the initial and final examinations was statistically significant.

Exophthalmos: Moore,[228] in 1920, stated that it is "undeniable that increase of orbital fat is the usual cause of the exophthalmos of Graves's disease." His opinion was based on finding an increase in fat both in a patient on whom he performed an autopsy and in another patient in whom he "picked away piecemeal as much orbital fat as possible" to treat severe proptosis. In the surgical case, he noted that the extraocular muscles were "greatly swollen" but did not consider the abnormality a contributing factor for exophthalmos. Rundle and Pochin[229] published in 1945 the results of a pathologic study in which the fat content in the orbital tissues was measured; they concluded that exophthalmos and eyelid retraction were caused by increased orbital fat and fatty involvement of the levator palpebrae superioris, respectively. The advent of computed tomography and improved histopathologic techniques confirmed that proptosis in most patients results primarily from enlarged extraocular muscles and glycosaminoglycan deposition,[230] although in some patients the orbital fat compartment alone may be increased.[231,232]

Graves' disease is the most common cause of both bilateral and unilateral exophthalmos,[233-236] but the finding often does not correlate well with other

facets of GO and has been considered by several authorities to be a relatively insensitive diagnostic feature.[34,237-240] Despite its limited usefulness, proptosis is an easily measured variable, and several studies have documented globe position in both normal and pathologic states.

Drescher and Benedict[233] performed Hertel exophthalmometry on a group of 100 unselected normal subjects (representing "various age groups, body types, races and types of refractive errors") and calculated an average of 17.3 mm. Values more than 22 mm were considered abnormal, as were measurements between eyes of more than 2.5 mm. In more recent studies, Bogren and coauthors[241] determined that the mean Hertel measurement in healthy American whites was 16 mm (range, 10 to 23) and in healthy American blacks was 18 mm (range, 12 to 26), whereas Frueh and colleagues[242] calculated an average value for normal individuals of 16.3 and 16.1 mm for the right and left eyes, respectively. Frueh and coworkers also analyzed the measurements with regard to sex and age and found that the mean Hertel readings for men were significantly higher than those for women (16.9 mm for right eye and 16.8 mm for left eye versus 15.9 mm for right eye and 15.6 mm for left eye, respectively) and that exophthalmometry readings were less among persons aged 65 years or older than among persons aged 45 to 64 years. Kaye and colleagues[243] likewise found that globe position receded with advancing age. Exophthalmometry in normal Asian individuals, as reflected in a study from Japan of 558 persons by Amino and associates,[244] disclosed a normal value of 13.9 ± 1.9 mm.

Average exophthalmometry readings in patients with Graves' disease have varied from 16.6 ± 2.1 mm in the study by Amino and coworkers[244] to 20.6 ± 3.3 mm among 200 patients reviewed by Day[1] to 22.5 mm (right eye) and 21.9 mm (left eye) in the investigation by Frueh and coworkers.[242] The mean exophthalmometry measurements among the patients in the current study were 18.8 and 18.9 mm for the right and left eyes, respectively, at the initial examination, and these had increased to averages of 19.2 and 19.7 mm at the most recent follow-up visit. The lower values in this report, compared with the data from Frueh and colleagues,[242] probably reflect the white racial homogeneity of the study population.

Proptosis, along with other soft tissue signs, has been thought to improve over time regardless of treatment.[245-248] Although the statistically significant increase in proptosis among patients in the incident cohort contradicts this view, there is precedent for the trend in two studies that were not population-based. Hales and Rundle,[94] in their 15-year follow-up report of 104 patients with GO, noted that exophthalmometry measurements were unchanged in 75 patients (72%), increased by more than 2 mm in 24 patients (23%), and decreased by the same increment in only 5 patients (5%).

Streeten and coworkers[249] studied 122 patients with Graves' disease who underwent exophthalmometry annually for 3 to 19 years after correction of thyrotoxicosis (by radioiodine in 81% of patients); measurements remained stable in 97 patients (80%), increased 2 mm or more in 19 patients (16%), and decreased 2 mm or more in 7 patients (5.7%). (Note that no explanation was provided for the discrepancy in the number of patients: 97 + 19 + 7 = 123.)

Superior Limbic Keratoconjunctivitis: The description of superior limbic keratoconjunctivitis (SLK) as a discrete clinical entity is attributed to Theodore.[250-252] Its putative association with thyroid dysfunction originated in a letter to the editor in 1968 by Tenzel,[253] who noted that three of four patients with SLK had markedly increased serum levels of protein-bound iodine, although without clinical evidence of hyperthyroidism. Theodore[254] commented on this observation by stating that he had examined patients with either increased or decreased protein-bound iodine levels. Numerous authors subsequently described hyperthyroidism in patients with SLK; in some studies the prevalence of thyroid dysfunction was as high as 50%.[255-263] Conversely, other investigators have documented normal results of thyroid function studies in patients with this ocular abnormality.[264,265] A recent report[266] described identical twins, Hispanic women aged 32 years, in whom SLK developed at age 16 years in each patient. No evidence of dysthyroid or other autoimmune disease was found in either patient, leading the author to favor a genetic basis for SLK.

Four (3.3%) of the 120 incident cases in the current study had documented SLK at some point in their clinical course: 1 patient had the finding at both initial and final examination, 1 patient had SLK at the most recent examination only, and 2 patients had SLK at a single interim visit. This frequency is lower than might be expected if a true association between SLK and thyroid dysfunction exists. A study is in progress to investigate this issue.

Intraocular Pressure: Although Wessely,[267] in 1918, most likely was the first investigator to document abnormal intraocular pressure in a person with GO, Braley[268] is credited with noting (in 1953) that the pressure may change in various positions of gaze. The usefulness of this observation to facilitate the diagnosis of GO subsequently has been discussed by several authors.[29,239,269-275] Reader,[276] however, measured intraocular pressure in normal subjects at 5-degree steps from 20 degrees upgaze to 20 degrees downgaze and found that the pressure may change as much as 7 mm Hg when gaze is changed from 0 degrees (primary gaze) to 20 degrees upgaze. He cautioned against diagnosing restrictive ophthalmopathy on the basis of an increase of 3 mm Hg in intraocular pressure on upgaze. At our institu-

tion, intraocular pressure in upgaze typically has not been measured routinely unless the diagnosis of ophthalmopathy is questionable. In such cases, an increase of at least 3 mm Hg is considered positive but not pathognomonic evidence in favor of extraocular muscle involvement. Because most patients have other, more definitive signs on which a diagnosis of GO can be made or excluded, only a few patients among the incidence cohort had such differential measurements.

The average intraocular pressures in primary gaze for the right and left eyes at the time of diagnosis of GO were 16.4 and 16.2 mm Hg, respectively, whereas at the last examination the respective readings were 16.5 and 16.6 mm Hg; the change was not significant. The distribution of intraocular pressures was nongaussian, with a slight skew toward higher values, a pattern that has been documented in normal subjects.[277] When analyzed by sex, intraocular pressure measurements in males were similar to those reported from the Beaver Dam Eye Study, a population-based study of predominantly white (99.4%) persons 43 to 86 years of age.[278] The mean intraocular pressure among the right eyes of 2,135 men in the Beaver Dam Eye Study was 15.3 ± 3.4 mm Hg, which was not statistically significantly different from the average right eye intraocular pressure in the current study either at the time of diagnosis of GO (16.1 ± 4.1 mm Hg; $P = .38$; two-sample t test) or at the final examination (16.1 ± 2.4 mm Hg; $P = .46$; two-sample t test). In contrast, the mean intraocular pressure in the right eyes of women in the current study was significantly greater both at the time of diagnosis of ophthalmopathy (16.4 ± 3.0 mm Hg; $P = .017$; two-sample t test) and at the last visit (16.6 ± 2.7 mm Hg; $P = .006$; two-sample t test) than the average intraocular pressure among the 2,721 women studied in the Beaver Dam study (15.5 ± 3.3 mm Hg). Conceivably, orbital congestion from GO could increase intraocular pressure, but such an effect was not detected in the relatively small number of males in the current study.

Prognosis

Werner[167] stated in 1967 that "the natural course of the severe eye changes is generally a prolonged one, ending ultimately, and unpredictably, in spontaneous remission." Many investigators agree with this trend toward a generally favorable prognosis.[15,49,54,74,94,151,153]

Although seven patients (5.8%) in the incident cohort had Graves' optic neuropathy at some point during their clinical course, persistent diminution of vision occurred in only two eyes of two patients; the visual acuities were 20/30 and 20/60, and the latter eye also had a cataract. Such improvement, either spontaneously or as a result of therapy, has been noted previously by others.[69,120,279-282] In addition to optic nerve compromise, another poten-

tially serious threat to vision in patients with GO is corneal ulcer. Sattler,[237] in 1909, reviewed 74 cases of visual loss from this complication and described the futility of treatment in that era. That there were no corneal ulcers among the 120 incident cases presented herein confirms that, in contemporary practice, ocular exposure in patients with GO rarely progresses to ulceration.

Approximately one patient in four in the current study required medical or surgical therapy for GO. Five percent of patients were treated with systemic corticosteroids, and 20% of patients underwent one or more ophthalmic operations. The cumulative risk of requiring a surgical procedure was approximately 16% at 5 years and 22% at 10 years after the diagnosis of ophthalmopathy. The current investigation confirmed the finding of Kendler and coworkers[36] in their study of referred patients that persons older than 50 years tend to have worse ophthalmopathy than do younger patients.

Although the findings of the current study suggest that disease activity eventually resolves and that function generally improves, the long-term psychological sequelae of GO are notable. Fifty-two percent of the patients in the incident cohort who completed the follow-up survey perceived the appearance of their eyes as abnormal, a frequency that is remarkably similar to the observation of Hales and Rundle[94] in their 15-year follow-up report published in 1960: "The general appearance of the patients had improved greatly. . .although in about 50% of those who formerly had conspicuous eye changes ophthalmopathy was still obvious at follow-up." Additionally, 38% of the patients in the current investigation were unhappy with their ultimate appearance. A properly designed and executed study to determine quality-of-life variables would be helpful to understand the psychosocial effects of GO.

LIMITATIONS OF THE STUDY

An incidence study requires the complete and accurate ascertainment of all persons diagnosed with a disorder during a defined period. As regards the current investigation, incorrectly low numerical estimates of persons coming to medical attention are unlikely because the resources of the Rochester Epidemiology Project provide access to all inpatient and outpatient medical records for care provided to Rochester and Olmsted County residents and in nearby areas. The ascertainment of a diagnosis of GO outside Olmsted County before the index date, however, is more problematic. Physician visits outside southeastern Minnesota or before the patient moved to Olmsted County may not be detected through the comprehensive medical record. Thus, because some small proportion of the incidence cohort may have had

an undetected prior diagnosis, estimates of the incidence of first visit for GO may slightly overestimate the true incidence. Additionally, the cohort size of 120 cases may limit the ability to detect secular changes or may hinder accurate inferences about subgroups.

A second potential weakness of this study is that data collection was retrospective, although supplemented in part with information gained from the follow-up questionnaire. Information was not available for each variable being studied from each examination. For example, visual acuity was not quantitated at the time of diagnosis of ophthalmopathy for nine patients who were examined initially by endocrinologists. Although it would be reasonable to assume that vision in these patients was normal (because a formal ophthalmic examination would have been obtained if a patient had any visual complaint or if the endocrinologist suspected any abnormality), no data for these patients were included, perhaps skewing the available data slightly away from normal. The quality of the data that were available, however, was good because of the high level of interest in thyroid disease and ophthalmopathy among physicians at our institution and because most examiners recorded historical and clinical findings in a fairly standardized manner. Using the information and experience gained from the current project, the author and his colleagues are planning to initiate within the next year a prospective study with the goal of examining all patients in Olmsted County who are diagnosed within a 1-year interval with autoimmune thyroid disease to determine the incidence of ophthalmopathy among subtypes of thyroid dysfunction and to detail the clinical course at regular intervals over a follow-up period of at least 5 years. Such a study should allow better determinations and correlations of specific clinical and laboratory variables (eg, the possible relationship of serum thyroid hormones to eyelid retraction) at defined points after diagnosis. Although data from all available examinations were collected and analyzed for the current project, it was difficult to create composite portraits of the study population at defined intervals because of the variability of follow-up.

In addition to the 120 incident cases described herein, data were compiled from the medical records of 80 patients with GO from Olmsted County who were diagnosed before 1976 but who were examined during the study interval (1976 through 1990). Although this information could be used to estimate the prevalence of GO within a population-based setting, it would represent a lower bound because additional patients with the disorder may not have sought medical attention during the defined interval. It was elected, therefore, to restrict this thesis to the description of incident cases.

Despite these limitations, this study provides new information that should be clinically useful, for example, in counseling newly diagnosed patients with GO about possible prognosis. Additionally, epidemiologic investigations are becoming increasingly important to discussions of health care policy in the United States.

SUMMARY

Among incident cases of GO in Olmsted County, Minnesota:

GO affected females six times more frequently than males (86% versus 14% of cases, respectively). The age-adjusted incidence rate was 16 cases per 100,000 population per year for females and 2.9 cases per 100,000 population for males.

The peak incidence rates were bimodal, occurring in the age groups 40 to 44 years and 60 to 64 years in females and 45 to 49 years and 65 to 69 years in males. Among patients with GO, approximately 90% had Graves' hyperthyroidism, 1% had primary hypothyroidism, 3% had Hashimoto's thyroiditis, and 5% were euthyroid.

Eyelid retraction was the most common ophthalmic feature of autoimmune thyroid disease, being present either unilaterally or bilaterally in more than 90% of patients at some point in their clinical course.

Exophthalmos of one or both eyes affected approximately 60% of patients, restrictive extraocular myopathy was apparent in about 40% of patients, and optic nerve dysfunction occurred in either one or both eyes in 6% of patients with autoimmune thyroid disease. Only 5% of patients had the complete constellation of classic findings: eyelid retraction, exophthalmos, optic nerve dysfunction, extraocular muscle involvement, and hyperthyroidism.

Upper eyelid retraction, either unilateral or bilateral, was documented in approximately 75% of patients at the time of diagnosis of GO. Lid lag also was a frequent early sign, being present either unilaterally or bilaterally in 50% of patients at the initial examination.

At the time of diagnosis of GO, the most frequent ocular symptom was pain or discomfort, which affected 30% of patients. Some degree of diplopia was noted by approximately 17% of patients, lacrimation or photophobia was present in about 15% to 20% of patients, and 7.5% of patients complained of blurred vision. Decreased vision attributable to optic neuropathy was present in less than 2% of eyes at the time of diagnosis of GO.

Thyroid dermopathy and acropachy accompanied GO in approximately 4% and 1% of patients, respectively. Myasthenia gravis occurred in less than 1% of patients. Superior limbic keratoconjunctivitis was documented in less

than 4% of patients.

The median age at the time of diagnosis of GO was 43 years (range, 8 to 88). Among patients with hyperthyroidism, 61% developed ophthalmopathy within 1 year of the onset of thyrotoxicosis.

Symptoms and signs for which statistically significant changes occurred between the initial and final examinations included lacrimation, pain or ocular discomfort, photophobia, eyelid retraction, lid lag, eyelid fullness, conjunctival injection, chemosis, and exophthalmos. The frequency, grade, or amount of all symptoms and signs decreased from the initial to the final examination, with the exception of exophthalmos, which increased.

In 20% of patients, one or more surgical procedures were used to treat GO. The median time between diagnosis of ophthalmopathy and the initial operation was 2.7 years. The cumulative probability of undergoing ophthalmic surgery was 5% by 1 year after diagnosis of ophthalmopathy, nearly 10% by 2 years, 16% by 5 years, and 22% by 10 years. Patients older than 50 years were more likely to have operation than patients 50 years or younger.

Persistent visual loss from optic neuropathy occurred in two eyes, with final visual acuities of 20/30 and 20/60. Long-term follow-up identified no patients with constant diplopia that was not correctable with spectacles. However, more than 50% of patients perceived their eyes as appearing abnormal, and 38% of patients were dissatisfied with the appearance of their eyes.

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APPENDIX 1

THE EVOLUTION OF CLASSIFICATION SCHEMES FOR GRAVES' OPHTHALMOPATHY

There is "a profound movement of the human spirit that can tolerate only with difficulty diverse things that cannot be classified."[52]

Mulvany,[53-55] in a seminal series of articles in 1944, classified "endocrine exophthalmos" into two categories: "thyrotoxic" (which was thought to be dependent on hyperthyroidism) and "thyrotrophic" (ophthalmopathy that is independent of thyroid status). In the same year, Means[56] also recognized that some patients have characteristic eye changes without accompanying detectable thyroid dysfunction. He and his colleagues at the Massachusetts General Hospital classified patients either as the "classic type" or as the "special ophthalmopathic type."

Wybar[57] conducted an extensive review of published works on Graves' ophthalmopathy (GO) in 1957 and concluded that "opinion is divided on a classification of the exophthalmos of Graves' disease." Vail's[58] comments in 1961 succinctly summarized the quandary: "The confusion in terminology reflects the confusion in the understanding of Graves' disease. The pathogenesis, or the trigger mechanism of thyrotropic, thyrotrophic, paradoxic, malignant, ophthalmoplegic, ophthalmopathic, hyperophthalmopathic, pituitary-diencephalic, endocrine, progressive exophthalmos—all of these terms are found in the literature—is moot. I can add here another term if you agree, and call this condition, à la Hollywood, 'super-colossal exophthalmos.'"

In 1969, Werner[42] presented on behalf of the American Thyroid Association detailed classification systems for both thyroid disease and thyroid-related eye disease. Thyroid dysfunction was segregated into three broad categories: diseases primarily characterized by euthyroidism, hyperthyroidism, or hypothyroidism. Among patients who were euthyroid and had Hashimoto's thyroiditis, a subgroup of individuals (I.F.1.b.) were identified "with eye changes of Graves' disease." Under the heading of hyperthyroidism, in which Graves' disease was termed "toxic diffuse goiter," two subgroups of patients with ophthalmic disease were categorized: II.A.1. ("with eye changes [ophthalmopathy]") and II.A.6. ("with euthyroidism and eye changes").[59]

Werner's[42] comments about the original intent of the NOSPECS classification system are notable, particularly in light of subsequent use of the scheme: It "is in no way intended as an aid in differential diagnosis or in the recording of the signs and symptoms of the eye involvement. It is solely a classification which summarizes the

situation after the diagnosis has been documented." The system comprised seven classes designated as 0 through 6 and was based on the following signs and symptoms: stare, lid lag and/or proptosis, sandy sensation, lacrimation, photophobia, conjunctival injection, chemosis, lid fullness, lagophthalmos, proptosis, diplopia, extraocular muscle involvement, corneal involvement, and optic nerve involvement. Class 0 represented the absence of eye changes, and class 1 denoted "the primarily cosmetic extreme of eye changes formerly called 'mild' or 'noninfiltrative,' and which carries an excellent prognosis. Classes 2 to 6 represent the severe eye changes with a potentially serious prognosis, formerly called 'severe,' 'infiltrative,' 'progressive,' or 'malignant,' etc." Each class could then be "subgraded to indicate absent, minimal, moderate or marked" disease and the "activity of the disease process is designated as active, static, or inactive, ie, in remission." Newell suggested that visual acuity levels be quantitated for the subgrades of class 6 (sight loss due to optic nerve involvement).[42]

Although at a major symposium on GO held 3 years later in 1972 at the Mayo Clinic the disorder was still designated by some authorities[60] as "noninfiltrative" or "infiltrative," Werner[14] noted that the NOSPECS system was gaining greater favor and reiterated the utility of the classification scheme, particularly regarding the use of the grades to subdivide the classes.

Donaldson and colleagues[43] published in 1973 an ophthalmopathy index that subsequently has been used either in its original or in a modified form by many investigators[35,37,61-66] for classification and grading. The index was calculated by scoring each class of the original American Thyroid Association classification as 1 = minimal, 2 = moderate, or 3 = marked. For proptosis, 1 = 20 to 23 mm, 2 = >23 to 27 mm, and 3 = more than 27 mm. Because only classes 2 through 6 ["SPECS"] were treated in their study, the maximal score, therefore, would be 15. More recently, authorities have criticized the validity of this index. For example, Bahn and Gorman[49] noted that the score actually may decrease if soft tissue signs improve even though optic neuropathy develops. Wiersinga and coworkers[67] demonstrated, by conducting a survey of attendees at the International Symposium on Graves' Ophthalmopathy held in Amsterdam in August 1991, that there is a wide variation in grading between observers.

Returning to Werner,[44,45] he presented in 1977, again on behalf of the American Thyroid Association, several modifications of NOSPECS. Additional commentary was included in a book chapter published the following year.[68] First, it was noted that one or more classes may be skipped because the eye disease often does not sequentially follow each class as it evolves. Second, because results of orbital computed tomography and ultrasonography were considered usually to be abnormal when proptosis exceeds 22 mm, class 1 (signs only) was modified "to include proptosis up to 22 mm, but not beyond. Proptosis in excess of 22 mm, even without symptoms, is placed in class 3."[44] In the original classification system, grade "o" denoted absent proptosis (≤ 20 mm), grade "a" indicated minimal exophthalmos (21 to 23 mm), grade "b" was used for moderate proptosis (24 to 27 mm), and grade "c" indicated marked proptosis (28 mm) or more. A discrepancy of 3 mm or more between the patient's two eyes but with proptosis of 22 mm or less remained in class

1. Third, class 3 (proptosis) was graded by millimeters above normal (which was defined as 20 mm), rather than the actual measurement. Fourth, it was recognized that the normal upper limits of proptosis are affected by ethnic factors, for example, 18 mm for Japanese and 22 mm or more for blacks. Additionally, it was noted that myopia may cause proptosis of more than 22 mm.

An "ophthalmopathy index" derived from the 1969 American Thyroid Classification system was used by Trobe and associates[69] in a study published in 1978. Each of four clinical signs was rated as minimal (1 point), moderate (2 points), or marked (3 points). The graded signs included proptosis (minimal = 20 to 23 mm; moderate = 24 to 27 mm; marked = more than 27 mm), restriction of ocular motility (minimal = 20 degrees; moderate = 10 to 20 degrees; marked = 10 degrees), keratitis (minimal = inferior one-third staining; moderate = central staining; marked = central erosion or ulcer), and soft tissue swelling and injection (which was graded qualitatively). The total points were added to calculate the index score.

Sergott and colleagues[70] noted in 1979 that the American Thyroid Association classification did not include provision for disease activity. They recognized in their own study and in the work of Solomon and coworkers[22] that there was an immunologic subgrouping within the clinical entity of euthyroid Graves' disease. In particular, Sergott and coworkers[70] found that within NOSPECS classes 4 and 5, the patients who had the best response to corticosteroid therapy for painful restrictive ophthalmoplegia had statistically significant decreased percentages of peripheral blood active rosette-forming cells and total rosette-forming cells. They concluded that there was a "need to incorporate an assessment of disease activity into the American Thyroid Association classification of the eye changes of Graves' Disease, since patients with red, inflamed eyes with progressive proptosis and worsening, painful ophthalmoplegia (class 4-5) differ clinically and immunologically from patients with white and quiet eyes with a fixed amount of proptosis and unchanging ocular motility (class 4-5, inactive)."

In 1981, Van Dyk[46] wrote that he agreed with the criticism by Sergott and associates[70] that disease activity could not be specified by the 1977 modification of NOSPECS and additionally believed that the new classification had been weakened by the omission of criteria for grading of class 2: "There is no longer a catalog of soft-tissue signs." His response was to propose a second modification that included assessment of signs, but not of symptoms, of soft tissue involvement in class 2. The first letters of the six signs spell the mnemonic RELIEF:

1. Resistance to retrodisplacement
2. Edema of conjunctiva and caruncle
3. Lacrimal gland enlargement
4. Injection of the conjunctiva ("a sensitive sign of disease activity")
5. Edema of lids
6. Fullness of lids ("lid fullness reflects edema and infiltration behind the orbital septum, whereas lid edema reflects fluid anterior to the orbital septum, just under the skin and orbicularis muscle")

The grading within class 2 was retained to permit a determination of the activity of the disease process. van Dyk concluded that "there is no entirely satisfactory

classification of this enigmatic orbital process possible until more is learned about the pathogenesis and the disordered immunology of the process. Until then, we will have to make do with a purely clinical classification."

Sergott and coworkers,[71] also in 1981, attempted to devise a clinical disease activity index that correlated with immunologic parameters. They noted that "The five clinical determinations found to be the best indicators of active, progressive ophthalmopathy in Werner's class 4 to 5 were (1) injection over the horizontal extraocular muscles; (2) pain with ocular motility, especially on attempted upgaze; (3) increased resistance to retropulsion of the globes; and for patients in class 6 (4) decreased Snellen visual acuity and (5) acquired dyschromatopsia documented by Ishihara pseudoisochromatic color plates." Parameters 1, 2, and 3 were graded from 0 to 4+. For parameter (4), "Best corrected visual acuity of 6/9 or less in one eye in a patient without a prior history of impaired vision or a decrease in visual acuity of two lines on the Snellen chart was given a score of 4+. There was no attempt to grade loss of visual acuity from 0 to 4+—a patient either maintained or lost vision." For parameter (5), a score of 0 to 4+ was given according to the number of color plates correctly identified.

If the activity index of Sergott and colleagues is correlated with NOSPECS, a maximal score of 12 could be assigned to patients in class 4 to 5 (without optic neuropathy), whereas patients in class 6 could have a maximal score of 20.

In 1982, Feldon and colleagues[47,72] proposed a system in which clinical severity was determined by the following seven signs:

1. Proptosis was "mild" if Krahn exophthalmometric readings were 22 to 24 mm or if asymmetry was 2 to 4 mm, "moderate" if readings were 24 to 27 mm or if asymmetry was 4 to 6 mm, and "severe" if readings were greater than 27 mm or asymmetry was greater than 6 mm.

2. Lid retraction was judged "mild" if the upper lid margin was 0 to 2 mm above the limbus with the eyes in primary position, "moderate" if the lid margin was 2 to 3 mm above the limbus, and "severe" if the lid margin was more than 3 mm above the limbus.

3. Lid lag was "mild" if retraction increased less than 2 mm in full downgaze, "moderate" if retraction increased 2 to 4 mm, and "severe" if retraction increased more than 4 mm.

4. Horizontal oculomotor dysfunction was considered "mild" if a phoria or phoria-tropia did not exceed 12 prism diopters (PD) or if ductions were limited less than 20%, "moderate" if phoria-tropia was 12 to 30 PD or if ductions were limited less than 50%, and "severe" if tropia exceeded 30 PD or if ductions were limited more than 50%. High-resolution infrared oculography was used to determine peak velocities for horizontal eye movements between 3 and 30 degrees.

5. Vertical oculomotor dysfunction was "mild" if phoria or phoria-tropia was less than 6 PD or if ductions were limited less than 20%, "moderate" if the phoria-tropia or tropia was 6 to 15 PD or if ductions were limited 20% to 50%, and "severe" if tropia was more than 15 PD or ductions were limited by more than 50%.

6. Optic nerve involvement was considered "mild" if there were nerve fiber layer

defects or hyperemia of the disc with blurred margins and visual acuity was best corrected to better than 20/30, "moderate" if there was mild disc pallor or optic nerve edema with venous engorgement and acuity better than 20/60, and "severe" if there was easily discernible disc pallor or well-developed swelling of the nerve head and acuity was less than 20/60.

7. Periorbital edema was judged "mild" if it did not thicken the upper or lower lid by more than 1 mm, "moderate" if lid thickening was 1 to 3 mm, and "severe" if lid thickening was more than 3 mm.

Feldon and coworkers grouped patients into class 1 if there were no severe signs and no more than one moderate sign; class 2 if there was one severe criterion, at least two moderate criteria, or both; or class 3 if there were severe criteria for at least two signs.

Kelly and coworkers,[73] in a 1983 study on the effect of plasma exchange on the severity of GO, devised a rating scheme that included 17 (admittedly overlapping) clinical or diagnostic features: ultrasonography (to determine extraocular muscle "width"), binocular single vision, intraocular pressure in primary gaze, intraocular pressure in upgaze, Hess chart, eyelid retraction, eyelid puffiness, exophthalmos of the right eye, exophthalmos of the left eye, chemosis, cornea (degree of superficial punctate keratopathy), computed tomography (to detect extraocular muscle enlargement), palpebral aperture, eyelid closure, eyelid lag, visual acuity, and optic disc appearance. Each parameter was graded as better, worse, or unchanged after therapy.

In 1983, Bartalena and coworkers[62] modified the ophthalmopathy index of Donaldson and associates[43] regarding the measurement and interpretation of exophthalmos: "values in the more prominent eye [>20 mm; ie, >3 mm above the normal limit (17 mm ± 2 SD)] were considered indicative of significant proptosis, and the score was calculated as follows: <20 mm = 0; 20-21 mm = 1; 21.5-24 mm = 2; and >24 mm = 3."

Feldon,[74] in 1984, opined that "there is no adequate classification of dysthyroid ophthalmopathy based on clinical signs. The well-known classification adopted by the American Thyroid Association, commonly referred to as 'NO-SPECS,' has proved of little value in understanding this disease." Also in 1984, Feldon and coworkers[75] performed a study in which they quantitated nine clinical signs (adduction, abduction, supraduction, infraduction, lid retraction, eyelid lag, periorbital swelling, proptosis, and optic nerve involvement) and correlated them with extraocular muscle volume. Statistically significant associations were found for horizontal, vertical, and total extraocular muscle limitation; periorbital swelling; and proptosis. Optic nerve involvement correlated with both total extraocular muscle volume and limitation of ocular motility. The investigators proposed that GO is best classified according to limitation of extraocular movements.

Glaser,[20] in an editorial in 1984, agreed with Feldon's reservations about the usefulness of NOSPECS and the need for more precise criteria for diagnosis and classification: "The Werner classification of the American Thyroid Association (ATA) falls far short of clinical usefulness in ophthalmic practice. With minor signs of stare,

lid retraction, and minimal proptosis, patients are more often diagnostic than therapeutic problems. . . .[the] Classification of Graves' ophthalmopathy is complicated and certainly not represented by a progressive continuum from the ATA class 0 ('no physical signs or symptoms') through class 3 ('proptosis. . .with or without symptoms') to class 6 ('sight loss caused by optic nerve involvement'). Lumping by highest common denominator has limited value. The 'ophthalmopathy index' of Trobe and colleagues[69] proved pragmatic for classifying patients with optic neuropathy. . . .[and] approaches a numerical equivalent of muscle volume changes in the orbit, as now described by Feldon and associates.[75] Next, no doubt, will be an ultrasonographic classification and, eventually, an immunologic system of grading Graves' ophthalmopathy."

A different tack was proposed by Kahaly and coworkers,[48] who in 1986 devised an activity score that included anamnestic information. The activity score was calculated as the sum of the following:

Subjective symptoms:	
photosensitivity	(1)
lacrimation	(1)
headache	(1)
feeling of retroocular pressure	(1)
foreign body sensation	(1)
Objective symptoms [sic]:	
palpebral edema	(1)
eyelid closure	(1)
sicca syndrome	(1)
chemosis	(1)
conjunctivitis	(1)
corneal ulceration	(1)
weak convergence	(1)
blurred vision	(2)
double vision	(2)
visual acuity	(2)
restriction of visual field	(2)
Hertel (20/23/26/more)	(2/4/6/8)
Imaging techniques:	
orbit sonography	(2)
orbit computed tomography	(4)

Proptosis was graded as follows: "≤20 mm = grade 0 = 2 points; 21-23 mm = grade A = 4 points, etc." and muscle thickness was rated with 2 points if identified by computed tomography or ultrasonography. This index has been criticized for giving disproportionate weight to soft tissue involvement.[66]

Bahn and Gorman,[49] recognizing that the extant classification systems had weaknesses when used to describe the results of treatment, suggested in 1987 that such results be reported using objective criteria only, excluding soft tissue changes that may be highly variable from day to day. The following criteria were proposed:

1. Proptosis

2. Extraocular muscle function
   Grade I: intermittent diplopia, present only when patient is fatigued
   Grade II: inconstant diplopia, present only on lateral or upward gaze
   Grade III: constant diplopia, present in primary gaze but correctable with prisms
   Grade IV: constant diplopia, present in primary gaze but not correctable with prisms
3. Optic nerve function (visual fields)
   Grade 0: both eyes normal
   Grade I: generalized constriction of field or impaired performance on color plates
   Grade II: visual field scotoma, not dense to the 35-mm target
   Grade III: visual field scotoma, dense to the 35-mm target
4. Visual acuity

Bartalena and colleagues[64] proposed in 1989 another modification of the ophthalmopathy index of Donaldson and coworkers[43] because they believed that the original index overestimated the importance of eyelid and conjunctival involvement and underestimated the manifestations that adversely affect sight, namely, optic neuropathy, corneal embarrassment, and extraocular muscle involvement. The chief changes involved the scoring values for proptosis, lagophthalmos, extraocular myopathy, and optic nerve involvement. Exophthalmos was given a higher score, particularly with measurements of more than 24 mm. A score for lagophthalmos was added because resultant corneal exposure may lead to visual loss. Restriction of ocular movements was assigned higher scores, and a new score for diplopia, in accordance with the criteria proposed by Bahn and Gorman,[49] was introduced. Evidence of optic neuropathy was assigned a greatly increased score. With the new index, the highest (worst) score obtainable was 30. Prummel and coworkers,[66] also in 1989, presented a similar modification of the ophthalmopathy index in which the higher classes or grades received proportionately more consideration.

In 1989, Mourits and colleagues[50] noted that inflammatory and noninflammatory GO respond differently to treatment and proposed a clinical classification system "based on the well known signs of acute inflammation: pain (Latin: dolor), redness (rubor), swelling (tumor), and impaired function (functio laesa), defined by Celsus and Galen centuries ago." Heat (calor) was omitted because an examiner could not diagnose it without sophisticated instruments.

Pain was defined as a painful, oppressive feeling on or behind the globe or pain on attempted eye movement. Pain from corneal defects, pain from spasm of the orbicularis secondary to photophobia, and pain from asthenopia due to a change in refractive error were considered epiphenomena and not useful in assessing disease activity. Redness was ascertained by the appearance of the eyelids or conjunctiva; IF the latter, it referred to diffuse erythema from vasodilation and was differentiated from redness secondary to exposure keratitis or vessel dilation over extraocular muscle insertions.

The definition of swelling was edema of the conjunctiva, caruncle, or eyelids, or an increase in proptosis of 2 mm or more during a period of between 1 and 3 months. Eyelid edema was differentiated from orbital fat prolapse anterior to the orbital septum or fibrotic degeneration. Impaired function was defined as a decrease in

visual acuity of 1 Snellen line (with pinhole) or more as a result of optic neuropathy (and not from corneal disease, another epiphenomenon) during a period of between 1 and 3 months, or a decrease of eye movements in any direction of 5 degrees or more during a period of 1 to 3 months. Color vision was not included because "testing patients with Ishihara pseudoisochromatic colour plates gives less reproducible results and does not provide more information than already gathered by testing the visual acuity."

Mourits and coworkers[50] commented on previous classification systems and activity scores. They found van Dyk's[46] NOSPECS modification flawed because two signs (resistance to retrodisplacement and lacrimal gland enlargement) do not indicate disease activity and thus are of questionable usefulness. The activity score proposed by Sergott and coauthors[71] was criticized because of its inclusion of resistance to retrodisplacement and dilated blood vessels over extraocular muscle insertions; the latter sign may occur with both progressive and quiescent ophthalmopathy and therefore was not considered useful for classification. The system advocated by Kahaly and coworkers[48] was considered imperfect because "signs and epiphenomena, such as eyelid closure and photosensitivity, are confused, while unchanging double vision and proptosis are included as signs of activity."

Disenchantment with NOSPECS continued into the 1990s. Rosen and Burde[16] noted that "clinically we have found it to be of little value," whereas Pope and McGregor[76] believed that the criteria "do not provide a sufficiently comprehensive picture of disease severity." The latter authors advocated a new "numerical 'ophthalmopathy index' (OI) which takes less account of subjective symptoms and more of objective physical signs and information derived from imaging of the orbit using computed tomography (CT) and ultrasound." Specifically, the index is the sum of assessments for several clinical signs (ophthalmoplegia, periorbital edema, chemosis, lid lag, lid retraction, visible insertion of extraocular muscles, conjunctival inflammation, proptosis of 20 to 23 mm or more than 3 mm difference between eyes, and proptosis of more than 23 mm). Although a maximal score of 11 could be assigned from the above findings, visual failure (as determined by decreased acuity, color vision, or a field defect) scored 11 irrespective of other signs.

Kahaly and coworkers[77] published a report in 1990 in which it was determined that urinary glycosaminoglycan excretion was significantly increased in patients with GO in comparison with control subjects. Additionally, glycosaminoglycans were found not to be abnormally increased in patients with Graves' hyperthyroidism without ophthalmopathy or in patients with inactive ophthalmopathy. Relapses, however, were accompanied by increased glycosaminoglycan excretion. Determination of urinary glycosaminoglycan excretion was considered "an effective parameter for the activity of Graves' ophthalmopathy." More recently, at a symposium on GO held in September 1992 in conjunction with the annual meeting of the American Thyroid Association, Kahaly and colleagues (abstract S-11) suggested that glycosaminoglycan levels in urine and plasma are "suitable for the routine assessment of disease activity and outcome of therapy." Urinary glycosaminoglycan excretion was significantly increased ($P < .005$) in patients with GO compared with control subjects, patients with Graves' hyperthyroidism without eye disease, and patients with

toxic nodular goiter. Increased levels were found in patients with active untreated eye disease compared with patients with inactive ophthalmopathy or in patients receiving immunosuppressive therapy. Plasma glycosaminoglycan levels were increased in all patients with ophthalmopathy compared with control subjects, and in patients with active eye disease the levels were increased threefold. Although these laboratory determinations hold promise as an indicator of disease activity, insufficient information is available to predict whether they will be of use in classifying various stages of the disease (G Kahaly, personal communication, September 22, 1992; written communication, March 29, 1993).

Nunery[78] subgrouped GO into type I (characterized by symmetry, lack of restrictive myopathy and diplopia, and minimal soft tissue signs) and type II (characterized by asymmetry, diplopia, soft tissue inflammation, and optic neuropathy). Nunery and associates believed that type II ophthalmopathy was not simply a more advanced stage of severity of type I disease, but rather that the two subtypes "represent distinct pathophysiologic entities."[79] They speculated that type I GO results from a circulatory factor that affects both orbits symmetrically, whereas type II disease is caused by retrograde flow of an as yet unidentified factor from cervical lymph nodes to one or both orbits. Although probably an unintentional error, the authors stated that the "subsets are distinguished by differing sexual predilection [*sic*]."[79] In any event, the proposed classification is not widely used.

Wiersinga and colleagues[67] described in 1991 the limitations of NOSPECS and its subsequent modifications; although the system is good for description (its original purpose), it is unsatisfactory for reporting treatment results: "Two patients with identical scores can be blind in one case and have a minimal cosmetic handicap in another." The authors noted the following requirements for an acceptable classification system: "It should be 1. Simple; 2. Purely clinical (ie, easily carried out by any physician equipped with ordinary noninvasive techniques); 3. Reproducible and meaningful (ie, as objective as possible and of clinical relevance to the patient)." Detailed, quantitative modifications to NOSPECS were proposed to improve its usefulness as a descriptive system. Alternatively, the authors believed that the activity score developed by their group[50] has "a high predictive value for the therapeutic outcome of immunosuppressive treatment."

Another experienced investigator, Devron Char,[80] wrote in 1991 that he does not use published classification systems for either patient categorization or treatment decisions because such systems "have almost no prognostic value" and that the data presented by numerical indices "are difficult to interpret" because different components of ophthalmopathy are not equal in terms of functional or cosmetic import.

Gorman,[81] in 1991, opined that "NOSPECS and related numerical indices are unsuited to recording the results of treatment for Graves' ophthalmopathy because they do not distinguish between primary causes and secondary events. They do not discriminate between what is important and what is not. They do not reflect the effectiveness of treatment directed toward only one component of the index." He argued that because "the fundamental cause of ophthalmopathy is unknown" and "all treatments are rehabilitative,". . ."an investigator should specify what benefits result from the therapy described and for each reported benefit the numerical data

that support the claim"; that is, the specific claims of each type of therapy (orbital decompression, corticosteroids, radiotherapy, strabismus surgery, eyelid surgery) should be evaluated by individual measurements, rather than being "diluted by application of the other index criteria."

In 1992, a consensus was achieved by committees representing the American Thyroid Association, the European Thyroid Association, the Asia-Oceania Thyroid Association, and the Latin-American Thyroid Association regarding the classification of GO.[51] It was agreed that NOSPECS should be retained as "an ingenious memory aid for the clinical examination of the orbital changes of Graves' disease" but that it and derivative numerical indices "are less satisfactory for objective assessment" of the clinical features of the disease and "for reporting the results of clinical studies." Rather, objective measurements should be reported, "relating to the status of eyelids, extraocular muscles, proptosis and optic nerve function." Feldon,[82] in subsequent correspondence to the journal *Thyroid,* suggested that eyelid retraction be accurately recorded by noting the relationship of both the upper and the lower lids to the respective corneoscleral limbus, proposed that eye ductions be measured in terms of a percentage of limitation, and commented on the proper technique for determining a change in intraocular pressure in upgaze.

The author of this thesis helped draft the consensus document (reference: letter dated October 15, 1991, from Dr CA Gorman to Drs WM Wiersinga, AAP Pinchera, M Izumi, and JH Romaldini) and followed its recommendations in conducting the current research project.

APPENDIX 2

Data Sheet Used at the Mayo Clinic to Record Information on Patients With Graves' Ophthalmopathy

Graves' Ophthalmopathy **Sheet No._____**

No._____ **Name_____** **Consulting Physician_____**

	Date		Date		Date	
Date and Sign	R	L	R	L	R	L
Pain						
Lacrimation						
Photophobia						
Blurring						
Diplopia: eyes straight						
eyes deviated						
Lid edema						
Chemosis						
Injection						
Lid lag						
Lid retraction						
Proptosis						
Exposure keratitis						
Corneal ulceration						
Papilledema						
Scotoma						
Muscle weakness						
Infiltrative dermopathy						
Blood drawn for:						
TSI, TSH, T4*						
Thyroid status						
Grouping (ATA)†						
Therapy						
Photo						

*TSI, thyroid-stimulating immunoglobulin; TSH, thyroid-stimulating hormone; T4, total thyroxine.
†ATA, American Thyroid Association.

APPENDIX 3

Laboratory Tests of Thyroid Function: Normal Values

Variable	Normal value	
Total thyroxine, μg/dl	Male	
	1-9 yr:	6.0-12.5
	10-17 yr:	5.0-11.0
	18-23 yr:	5.0-11.0
	≥24 yr:	5.0-12.5
	Female	
	1-9 yr:	6.0-12.5
	10-17 yr:	5.0-11.0
	≥18 yr:	5.0-12.5
Free thyroxine, ng/dl	0.7-2.0	
Triiodothyronine, ng/dl	1-14 yr:	125-250
	15-23 yr:	100-220
	≥24 yr:	80-180
		181-230 (borderline hyperthyroid)
Thyroid-stimulating hormone, μU/ml	0.5-6.0	
Sensitive thyroid-stimulating hormone, mIU/l	Male	
	1-19 yr:	0.4-7.0
	20-29 yr:	0.4-5.0
	30-39 yr:	0.4-5.5
	40-49 yr:	0.4-6.0
	50-59 yr:	0.4-7.0
	60-69 yr:	0.4-8.0
	70-79 yr:	0.4-9.0
	≥80 yr:	0.4-10.0
	Female	
	1-19 yr:	0.4-7.0
	20-29 yr:	0.4-5.0
	30-39 yr:	0.4-5.5
	40-49 yr:	0.4-6.0
	50-59 yr:	0.4-7.0
	60-69 yr:	0.4-8.0
	70-79 yr:	0.4-9.0
	≥80 yr:	0.4-10.0
^{131}I uptake, %	6 hr, 3-16	
	24 hr, 8-29	
Thyroid-stimulating immunoglobulin, TSI index	0.0-1.3 TSI	
Microsomal antibody titer	<1:100	
Thyroglobulin antibody titer	<1:100	