Medical Progress

GRAVES' DISEASE

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ROBERT Graves first identified the association of goiter, palpitations, and exophthalmos in 1835, although Caleb Parry had published details of a case 10 years earlier. The discovery of a thyroid-stimulating factor that was not thyrotropin in the serum of patients with Graves' hyperthyroidism[1] was followed by the identification of this stimulator as an IgG antibody.[2] It is now clear that Graves' hyperthyroidism is caused by these thyroid-stimulating antibodies, which bind to and activate the thyrotropin receptor on thyroid cells.[3] Graves' disease also affects the eyes (Graves' ophthalmopathy) and the skin (localized dermopathy or myxedema), but the causes of these less common components of the disease are not known.

PATHOGENESIS

Graves' disease shares many immunologic features with autoimmune hypothyroidism, including high serum concentrations of antibodies against thyroglobulin, thyroid peroxidase, and possibly the sodium–iodide cotransporter in thyroid tissue.[4] The serum concentrations of these antibodies vary among patients, and the antibodies themselves may modify the stimulatory effects of thyroid-stimulating antibodies. In some patients, the simultaneous production of antibodies that block the thyrotropin receptor reduces the stimulatory action of thyroid-stimulating antibodies. For these reasons there is no direct correlation between serum concentrations of thyroid-stimulating antibodies and serum thyroid hormone concentrations in patients with Graves' hyperthyroidism.[5] The thyroid-stimulating antibodies cause not only thyroid hypersecretion but also hypertrophy and hyperplasia of the thyroid follicles, which have a columnar and folded epithelium and little colloid.[6] The result is the characteristic diffuse goiter (Fig. 1A). Lymphocytic infiltration is often present, occasionally resulting in the formation of germinal centers. These intrathyroidal lymphocytes are a major source of autoantibodies, with contributions from the cervical lymph nodes and bone marrow.[7] Antithyroid drugs ameliorate the histologic changes.[8]

Autoimmunity to the Thyrotropin Receptor

The thyrotropin receptor is a member of the family of G protein–coupled receptors.[9] The mechanism by which thyroid-stimulating antibodies bind to and activate the thyrotropin receptor is not known,[10] but studies with mutated receptors and thyrotropin-receptor sequences have revealed that thyroid-stimulating antibodies bind to conformational epitopes in the extracellular domain of the thyrotropin receptor. These epitopes make up discontinuous segments that overlap the binding site for thyrotropin.[11,12] The production of thyroid-stimulating antibodies is dependent on T cells, and circulating T cells recognize multiple epitopes of the thyrotropin receptor.[13]

Although thyroid-stimulating antibodies cause Graves' hyperthyroidism, the serum antibody concentrations are very low[11] and are even undetectable in a few patients. The most likely reason for this finding is assay insensitivity, exclusively intrathyroidal production of the antibodies, or misdiagnosis (for example, when the patient actually has familial nonautoimmune hyperthyroidism). The hyperthyroidism and goiter are caused primarily by the ability of the thyroid-stimulating antibodies to increase the production of intracellular cyclic AMP. Some of these antibodies also activate phospholipase A_2, and antibodies with this activity may be especially goitrogenic.[14]

The Role of Thyroid Cells

In Graves' disease, thyroid cells not only are sources of thyroid antigens and the target of thyroid-stimulating antibodies, but also express several molecules that modulate intrathyroidal autoimmunity (Fig. 2). In response to interferon-γ produced by infiltrating T cells, the thyroid cells express HLA class II molecules, allowing the cells to present antigens such as the thyrotropin receptor to activated T cells.[15] Naive T cells, which require a costimulatory signal from antigen-presenting cells, do not respond to thyroid cells presenting antigen,[16] because the cells do not have the most important costimulatory molecules, CD80 and CD86, which stimulate T cells by means of CD28. Therefore, the initiation of Graves' disease is likely to involve dendritic cells and B cells that express CD80 and CD86. Later, the presentation of antigen by thyroid cells may exacerbate the autoimmune process, as

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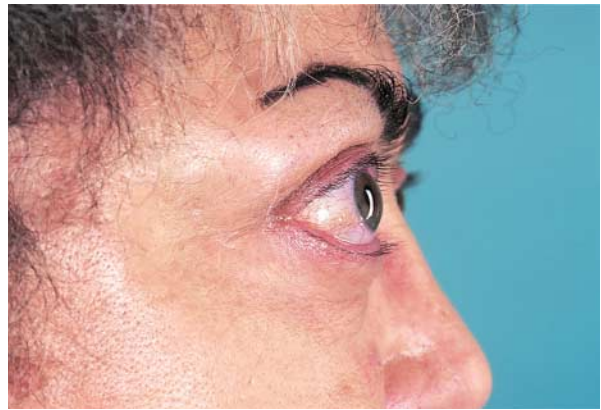
Figure 1. Clinical Manifestations of Graves' Disease.

Panel A shows diffuse goiter in a 28-year-old woman with Graves' hyperthyroidism. Panels B and C show ophthalmopathy in a 55-year-old woman with Graves' disease, with periorbital edema, chemosis, scleral injection, and proptosis; the lid retraction in this patient is obscured by periorbital edema. Panel D shows localized dermopathy, occurring as an indurated, noninflamed plaque on the anterolateral aspect of the shin of a 47-year-old woman.
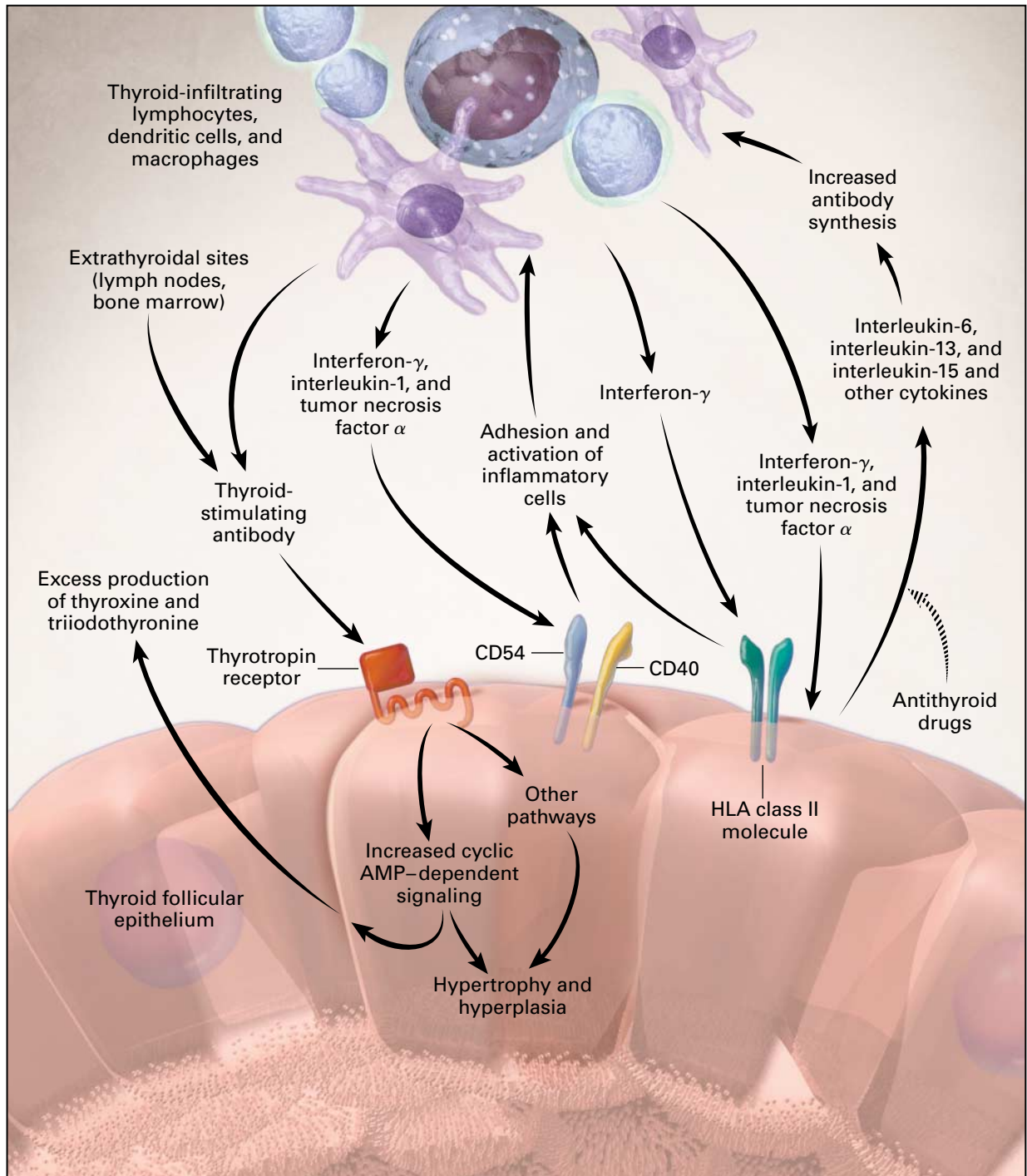
Figure 2. Pathogenesis of Graves' Disease.
Excess production of thyroid hormone is caused by the activation of thyrotropin receptors by thyroid-stimulating antibodies produced within and outside the thyroid gland. The intrathyroidal inflammatory cells also produce cytokines, such as interleukin-1, tumor necrosis factor α, and interferon-γ, that induce the expression of adhesion molecules such as CD54, regulatory molecules such as CD40, and HLA class II molecules, which in turn activate local inflammatory cells. These cytokines also induce thyroid cells to synthesize cytokines that may help sustain the intrathyroidal autoimmune process. Antithyroid drugs reduce the production of thyroidal cytokines — an ability that may explain their immunomodulatory effects (which include a decrease in the production of thyroid-stimulating antibody) — contributing to remission in some patients.

may the expression of other molecules by thyroid cells, such as CD40, CD54, and interleukin-1 and interleukin-6 (Fig. 2).[4]

Ophthalmopathy and Dermopathy

Graves' ophthalmopathy is characterized by edema and inflammation of the extraocular muscles and an increase in orbital connective tissue and fat.[17] The edema is due to the hydrophilic action of glycosaminoglycans secreted by fibroblasts. The inflammation is due to infiltration of the extraocular muscles and orbital connective tissue by lymphocytes and macrophages. The increase in the volume of retrobulbar tissue is responsible for most of the clinical manifestations of ophthalmopathy. The muscle cells are normal until the late stages of ophthalmopathy, when they may become atrophic or fibrotic. The muscle cells of the eyelid are hypertrophic but have little lymphocytic infiltration.[18] Dermopathy is characterized by lymphocytic infiltration of the dermis, the accumulation of glycosaminoglycans, and edema.[19]

The close relation between Graves' hyperthyroidism and ophthalmopathy suggests that both result from an autoimmune response to one or more antigens located in the thyroid and orbit.[20] The currently favored candidate antigen is the thyrotropin receptor, expressed by the preadipocyte subpopulation of orbital fibroblasts.[21] The only animal model of ophthalmopathy has been created by transferring thyrotropin-receptor–primed T cells to genetically susceptible mice.[22] In these animals the response to the thyrotropin receptor is mediated by type 2 helper T cells and characterized by the production of interleukin-4 and interleukin-10. In addition to orbital lymphocytic infiltration and edema, thyroiditis develops in these mice. These findings suggest that autoreactivity to the thyrotropin receptor causes ophthalmopathy. Why preadipocytes elsewhere in the body are not targeted by the autoimmune response is unclear, and other studies suggest that different orbital antigens may have a role.[23]

Regardless of the self antigen that causes the local accumulation of lymphocytes, the proximal events in the pathogenesis of ophthalmopathy and dermopathy appear to be cytokine-mediated activation of fibroblasts, secretion of glycosaminoglycans by these cells, and ultimately, fibrosis (Fig. 3). Ophthalmopathy has not yet been demonstrated convincingly in neonates who have Graves' hyperthyroidism as a result of the transplacental passage of maternal thyroid-stimulating antibodies, and the presence of antibodies to orbital antigens is inconsistently related to eye disease, indicating at most a secondary role for humoral autoimmunity in pathogenesis.

PREDISPOSING FACTORS

Susceptibility to Graves' disease is determined by a mixture of genetic, environmental, and endogenous factors, which are responsible for the emergence of autoreactivity of T and B cells to the thyrotropin receptor. The mechanisms involved are unknown.

Genetic Factors

The rate of concordance for Graves' disease is about 20 percent among monozygotic twins, and the rate is much lower among dizygotic twins, indicating that genes make only a moderate contribution to susceptibility.[24] No single gene is known to cause the disease or to be necessary for its development. There is a well-established association with certain HLA alleles that varies among racial groups. In whites, HLA-DR3 and HLA-DQA1*0501 are positively associated with Graves' disease, whereas HLA-DRB1*0701 protects against it.[25,26] The risk of Graves' disease in the HLA-identical siblings of an affected patient is much lower than the risk in a monozygotic twin,[24] indicating the involvement of non-HLA genes.

Graves' disease is associated with polymorphisms of the cytotoxic T-lymphocyte antigen 4 (*CTLA-4*) gene in several racial groups.[24,27] This association may reflect an effect of certain *CTLA-4* alleles on the function of autoreactive T cells, because other organ-specific autoimmune disorders are also associated with *CTLA-4* polymorphisms. When a CTLA-4 molecule, rather than a CD28 molecule, on a T cell engages CD80 or CD86 costimulatory molecules on antigen-presenting cells, the T cell is inactivated. Linkage analysis has identified loci on chromosomes 14q31, 20q11.2, and Xq21 that are associated with susceptibility to Graves' disease,[28-30] but confirmation of the importance of these loci will require screening large numbers of families with multiple affected members. There is no clear genetic susceptibility to the development of ophthalmopathy.

Environmental and Endogenous Factors

The chief risk factor for Graves' disease — female sex — is in part the result of the modulation of the autoimmune response by estrogen. In some patients, adverse events (such as bereavement, divorce, and job loss) precede the onset of Graves' disease, supporting the possibility of a role for stress as an initiating factor in the disease by means of neuroendocrine pathways.[31] Smoking is weakly associated with Graves' hyperthyroidism and strongly associated with the development of ophthalmopathy.[32] In regions of iodine deficiency, iodine supplementation precipitates Graves' hyperthyroidism and other types of hyperthyroidism, by means of the Jod–Basedow phenomenon. Lithium therapy is usually associated with hypothyroidism and goiter, but paradoxically, hyperthyroidism — including Graves' hyperthyroidism — may be induced by this treatment, possibly through the immunologic effects of the drug.[33]

In patients with the acquired immunodeficiency syndrome, highly active antiretroviral therapy has been associated with Graves' hyperthyroidism and may be
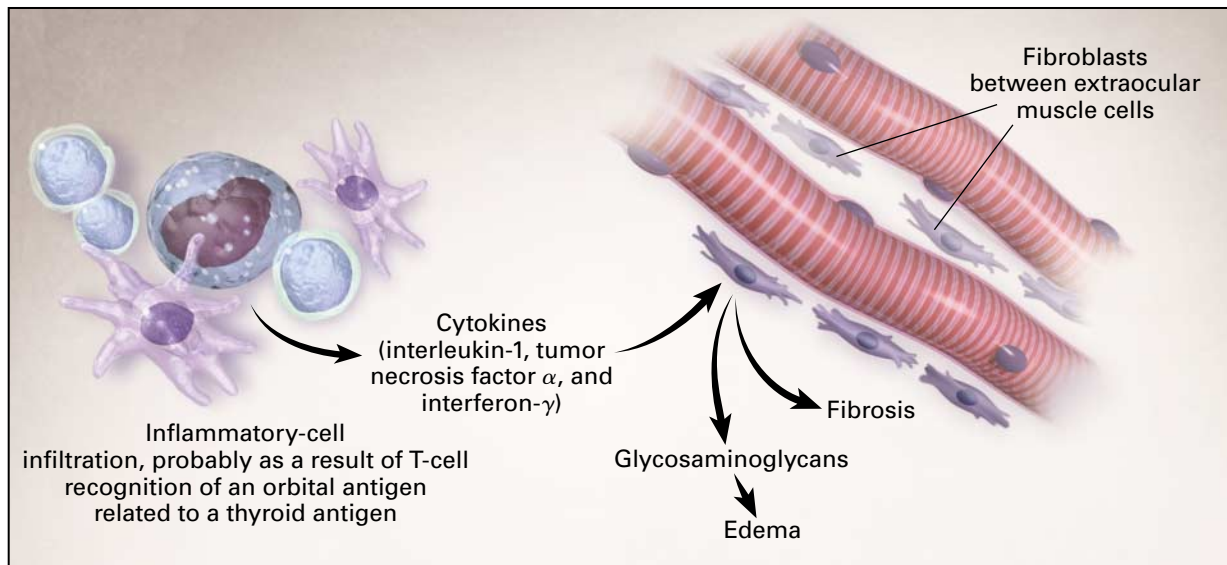
Figure 3. Pathogenesis of Graves' Ophthalmopathy.
There is an inflammatory-cell infiltrate composed predominantly of activated T cells in the extraocular muscles and orbital connective tissue. This infiltrate may localize in the orbit through the recognition by T cells of an orbital antigen that cross-reacts with a thyroid antigen, such as the thyrotropin receptor expressed in preadipocyte fibroblasts. Cytokines produced by the infiltrate activate fibroblasts, stimulating the production of glycosaminoglycans (mainly hyaluronate and chondroitin sulfate) and leading to edema and fibrosis.

related to the resulting increase in the numbers or change in the function of CD4+ T cells.[34] Graves' hyperthyroidism also occurs in patients with multiple sclerosis who are treated with the Campath-1H monoclonal antibody directed against T cells.[35] There is no evidence that infection affects the susceptibility to Graves' hyperthyroidism or directly induces it.[36]

EPIDEMIOLOGIC FACTORS

Among patients with hyperthyroidism, 60 to 80 percent have Graves' disease, depending on regional factors, especially iodine intake. The annual incidence in women over a 20-year period is around 0.5 per 1000,[37] with the highest risk of onset between the ages of 40 and 60 years; it is thus the most prevalent autoimmune disorder in the United States.[38] Graves' disease is 1/5 to 1/10 as common in men as in women and is unusual in children. The prevalence of Graves' disease is similar among whites and Asians, and it is lower among blacks.[37]

CLINICAL MANIFESTATIONS

The clinical manifestations of Graves' disease can be divided into those common to any form of hyperthyroidism and those specific to Graves' disease (Table 1).[39] The severity and duration of Graves' disease and the age of the patient determine the manifestations of hyperthyroidism. The most common symptoms are nervousness, fatigue, a rapid heartbeat or palpitations, heat intolerance, and weight loss; these symptoms are present in more than half of all patients who have the disease. With increasing age, weight loss and decreased appetite become more common, whereas irritability and heat intolerance are less common.[40] Atrial fibrillation is rare in patients who are younger than 50 years old but occurs in up to 20 percent of older patients. Approximately 90 percent of patients who are younger than 50 years old have a firm, diffuse goiter of variable size (Fig. 1A), as compared with about 75 percent of older patients.[40] Nonspecific laboratory findings include high serum concentrations of bilirubin, aminotransferases, ferritin, and sex hormone–binding globulin. The rate of bone resorption is increased. Hypercalciuria is frequent, but hypercalcemia is rare. Glucose intolerance and, rarely, diabetes mellitus may accompany hyperthyroidism. Among patients who are treated with insulin for diabetes, hyperthyroidism increases the insulin requirement.

Clinically evident ophthalmopathy (Fig. 1B and 1C) occurs in about 50 percent of patients, in 75 percent of whom the eye signs appear within a year before or after the diagnosis of hyperthyroidism. However, imaging studies reveal evidence of ophthalmopathy, in the form of enlarged extraocular muscles, in most patients without clinical signs.[41] Older men are at highest risk of severe ophthalmopathy.[42] The prevalence

of clinically evident ophthalmopathy is lower in Asians than in whites.[43] About 90 percent of patients with ophthalmopathy have hyperthyroidism; the remainder have autoimmune hypothyroidism or are euthyroid at presentation.

The most frequent signs of ophthalmopathy (Table 1) are eyelid retraction or lag and periorbital edema. Although a minor degree of eyelid retraction (1 to 2 mm) may be due to sympathetic overactivity and can occur in patients with any type of hyperthyroidism, more marked retraction is likely to be due to Graves' ophthalmopathy. Exophthalmos (proptosis) occurs in up to a third of patients, and diplopia occurs in 5 to 10 percent. Compression of the optic nerve at the apex of the orbit may cause visual loss but is rare. Clinicians can estimate the activity of the eye disease by awarding a point for each of the following signs: retrobulbar pain, pain on eye movement, eyelid erythema, conjunctival injection, chemosis, swelling of the caruncle, and eyelid edema.[44] This score can be used in addition to objective findings of worsening, including increasing proptosis, decreasing visual acuity, and decreasing eye movement, to assess the level of activity of ophthalmopathy.

Localized dermopathy is most frequent over the anterolateral aspects of the shin (Fig. 1D), but it can occur at other sites, especially after trauma.[45] Dermopathy occurs in 1 to 2 percent of patients with Graves' disease, almost always in the presence of severe ophthalmopathy.

DIAGNOSTIC STUDIES

Graves' Hyperthyroidism

The diagnosis of Graves' hyperthyroidism is based on the clinical and biochemical manifestations of hyperthyroidism and on the clinical and laboratory features that confirm the cause. Measurement of serum thyrotropin is a useful screening test for the presence of hyperthyroidism, because very small increases in thyroid secretion reduce the secretion of thyrotropin, but the diagnosis of hyperthyroidism must be confirmed by the measurement of serum free thyroxine.[46] Patients in the earliest stage of Graves' hyperthyroidism may have only increased secretion of triiodothyronine; therefore, serum free triiodothyronine should be measured in patients with normal serum free thyroxine concentrations and low serum thyrotropin concentrations. Measurements of serum total thyroxine and triiodothyronine are less reliable, because use of certain drugs and increases in thyroid hormone–binding proteins can cause high values. A scheme for establishing the diagnosis in a patient with hyperthyroidism is shown in Figure 4.

The signs of ophthalmopathy or dermopathy are sufficient to confirm the diagnosis of Graves' disease in a patient with hyperthyroidism and a diffuse goiter. Other autoimmune disorders occur more frequently in patients with Graves' disease (Table 1), and their

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TABLE 1. MAJOR SYMPTOMS AND SIGNS OF HYPERTHYROIDISM AND OF GRAVES' DISEASE AND CONDITIONS ASSOCIATED WITH GRAVES' DISEASE.

Manifestations of hyperthyroidism

Symptoms
  Hyperactivity, irritability, altered mood, insomnia
  Heat intolerance, increased sweating
  Palpitations
  Fatigue, weakness
  Dyspnea
  Weight loss with increased appetite (weight gain in 10 percent of patients)
  Pruritus
  Increased stool frequency
  Thirst and polyuria
  Oligomenorrhea or amenorrhea, loss of libido
Signs
  Sinus tachycardia, atrial fibrillation
  Fine tremor, hyperkinesis, hyperreflexia
  Warm, moist skin
  Palmar erythema, onycholysis
  Hair loss
  Muscle weakness and wasting
  Congestive (high-output) heart failure, chorea, periodic paralysis (primarily in Asian men), psychosis*

Manifestations of Graves' disease

Diffuse goiter
Ophthalmopathy
  A feeling of grittiness and discomfort in the eye
  Retrobulbar pressure or pain
  Eyelid lag or retraction
  Periorbital edema, chemosis, scleral injection
  Exophthalmos (proptosis)
  Extraocular-muscle dysfunction
  Exposure keratitis
  Optic neuropathy
Localized dermopathy
Lymphoid hyperplasia
Thyroid acropachy

Conditions associated with Graves' disease

Type 1 diabetes mellitus
Addison's disease
Vitiligo
Pernicious anemia
Alopecia areata
Myasthenia gravis
Celiac disease
Other autoimmune disorders associated with the HLA-DR3 haplotype

*These signs are rare.

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presence therefore supports this diagnosis. Occasionally, Graves' disease occurs in a patient with preexisting nodular goiter,[47] causing confusion. When the diagnosis is unclear clinically, the presence of a high serum concentration of thyroid peroxidase antibody, present in about 75 percent of patients with Graves' hyperthyroidism, or a thyroid radionuclide scan demonstrating a diffuse goiter provides evidence of Graves' disease. Occasionally, thyroid radionuclide studies may be indicated to distinguish between Graves' hyperthyroidism and thyrotoxicosis caused by painless, destructive (autoimmune) thyroiditis, especially in women post partum. Patients with painless thyroiditis, like those with Graves' disease, may have a small dif-
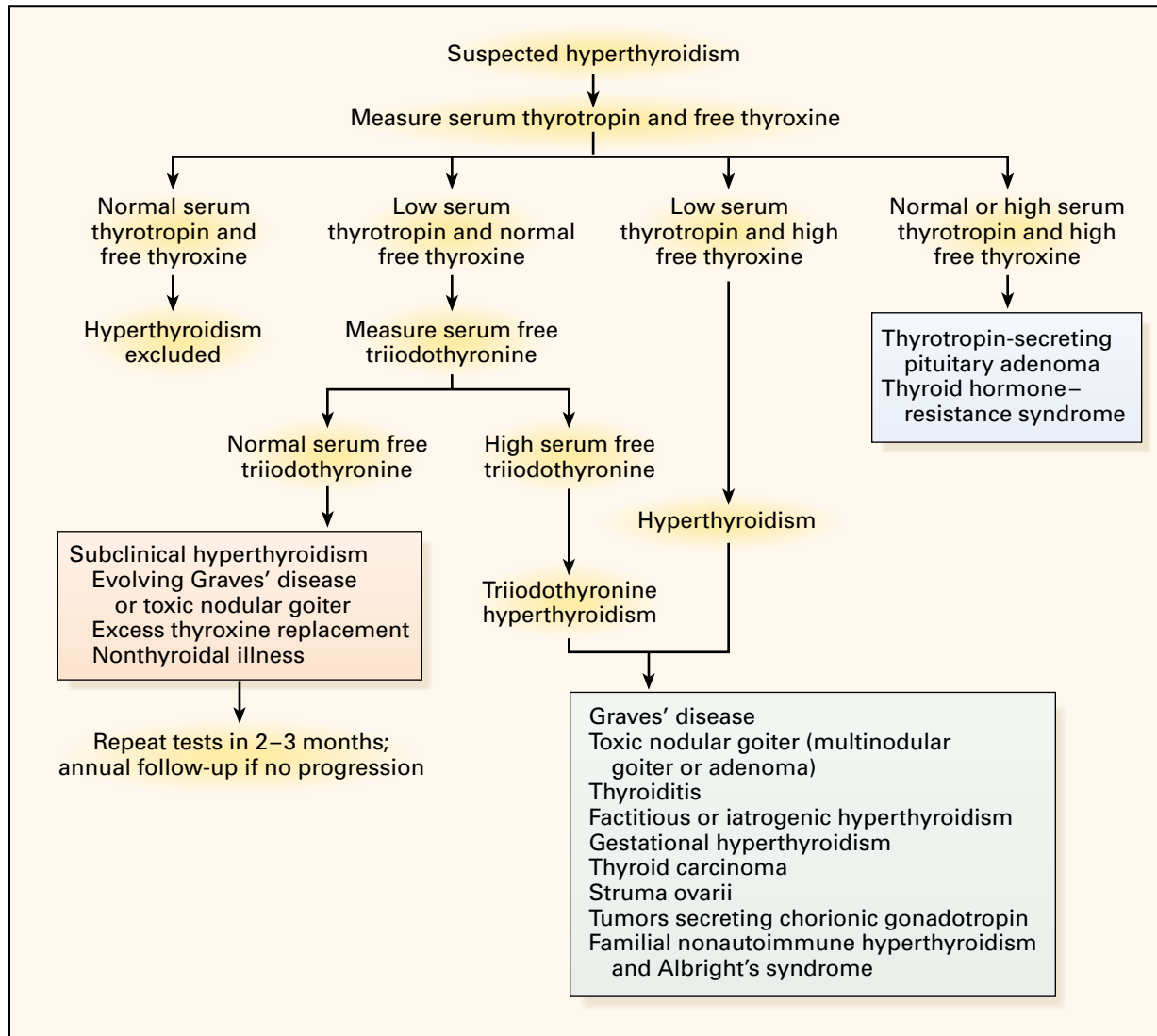
Suspected hyperthyroidism

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Measure serum thyrotropin and free thyroxine

| Normal serum thyrotropin and free thyroxine | Low serum thyrotropin and normal free thyroxine | Low serum thyrotropin and high free thyroxine | Normal or high serum thyrotropin and high free thyroxine |

Normal serum thyrotropin and free thyroxine → Hyperthyroidism excluded

Low serum thyrotropin and normal free thyroxine → Measure serum free triiodothyronine

Normal or high serum thyrotropin and high free thyroxine →
Thyrotropin-secreting pituitary adenoma
Thyroid hormone–resistance syndrome

Measure serum free triiodothyronine →
- Normal serum free triiodothyronine
- High serum free triiodothyronine

Normal serum free triiodothyronine →
Subclinical hyperthyroidism
Evolving Graves' disease or toxic nodular goiter
Excess thyroxine replacement
Nonthyroidal illness
→ Repeat tests in 2–3 months; annual follow-up if no progression

High serum free triiodothyronine → Triiodothyronine hyperthyroidism

Low serum thyrotropin and high free thyroxine → Hyperthyroidism

Hyperthyroidism / Triiodothyronine hyperthyroidism →
Graves' disease
Toxic nodular goiter (multinodular goiter or adenoma)
Thyroiditis
Factitious or iatrogenic hyperthyroidism
Gestational hyperthyroidism
Thyroid carcinoma
Struma ovarii
Tumors secreting chorionic gonadotropin
Familial nonautoimmune hyperthyroidism and Albright's syndrome

Figure 4. Approach to Establishing the Diagnosis in a Patient with Clinical Manifestations of Hyperthyroidism.

fuse goiter. However, thyrotoxicosis due to painless thyroiditis is very unlikely to last longer than two months.

Measurement of Thyrotropin-Receptor Antibodies in Serum

Whether serum thyrotropin-receptor antibodies should be measured in the differential diagnosis of Graves' disease is largely a matter of individual preference[48]: some argue that a test for the antibodies should be done routinely, and others that a diagnosis of Graves' disease can nearly always be inferred correctly on the basis of the clinical findings. The most widely used assay for thyrotropin-receptor antibodies is based on immunoglobulin-mediated inhibition of the binding of radiolabeled thyrotropin to thyrotropin receptors[49] and is positive in about 80 percent of patients with Graves' hyperthyroidism. New assays have higher sensitivity (up to 99 percent).[50] Although a positive result may indicate the presence of either thyroid-stimulating antibodies or thyrotropin-receptor–blocking antibodies, it is reasonable to conclude that a positive test in a patient with hyperthyroidism is due to thyrotropin-receptor–stimulating antibodies.

As the understanding of the interactions of antibodies with the thyrotropin receptor improves,[3,10] it should be possible to develop simple, specific immunoassays for thyroid-stimulating antibodies for routine use. Only thyroid-stimulating antibodies are detected by bioassays that measure the production of

cyclic AMP in response to the stimulation of thyrotropin receptors — for instance, in cells transfected with thyrotropin receptor[51] — but such assays are relatively expensive and not widely available.

Ophthalmopathy

Computed tomography (CT) or magnetic resonance imaging (MRI) of the orbits is indicated if there is any uncertainty about the cause of ophthalmopathy, particularly in a patient with unilateral exophthalmos, to rule out a retrobulbar tumor or arteriovenous malformation. There is no consensus on the best combination of tests for the assessment of the activity or severity of ophthalmopathy.[52] Methods to assess the activity of ophthalmopathy are helpful in determining which patients will benefit from immunosuppressive treatment. Clinical activity scores,[44] measurement of the relaxation time for extraocular muscles on T_2-weighted MRI,[53] and orbital scanning with indium In 111 pentetreotide[54] have all been advocated for this purpose but have not been fully evaluated. These tests are not required for the majority of patients, who have only mild or moderate Graves' ophthalmopathy.

NATURAL HISTORY

Since effective treatments are available, it is now impossible to establish the natural history of Graves' disease in patients who are not given antithyroid therapy. About 20 percent of patients with mild hyperthyroidism who are treated with beta-adrenergic antagonists for one year will become clinically and biochemically euthyroid, but the frequency of permanent euthyroidism is unknown. Thirty to 40 percent of patients who are treated with an antithyroid drug remain euthyroid for prolonged periods after the drug is discontinued. In about 15 percent of these patients, autoimmune hypothyroidism develops 10 to 15 years later.[55] The course of Graves' ophthalmopathy is largely independent of thyroid status, although it tends to be more severe in patients in whom hyperthyroidism is poorly controlled.[56] Typically there is a period of worsening over 12 to 18 months, followed by a period of stabilization; spontaneous improvement of mild ophthalmopathy occurs in approximately 60 percent of patients.[57] However, unpredictable and sudden worsening of ophthalmopathy can occur at any time, independently of antithyroid therapy.

THERAPY

The ideal treatment for Graves' disease, which would correct the autoimmune responses in the thyroid and orbits, thereby restoring thyroid function and resulting in the disappearance of ophthalmopathy, is not available. Current treatments for Graves' hyperthyroidism consist of antithyroid drugs, radioactive iodine, and surgery. There is regional variation in their use — for example, radioactive iodine is favored in

North America and antithyroid drugs nearly everywhere else. Because immunosuppressive treatments are nonspecific and incompletely effective and have important side effects, patients with mild or moderate ophthalmopathy are usually treated with local measures, despite the associated psychosocial problems.[58] The treatment of hyperthyroidism and ophthalmopathy has been described in detail elsewhere,[59-61] and an overview is provided in Tables 2 and 3.

Antithyroid Drugs

Carbimazole, its active metabolite methimazole, and propylthiouracil all inhibit thyroid peroxidase and thus the synthesis of thyroid hormone. Propylthiouracil also blocks the extrathyroidal deiodination of thyroxine to triiodothyronine, which may lead to a more rapid initial reduction in serum triiodothyronine concentrations and possibly to a more rapid resolution of symptoms of hyperthyroidism, as compared with the other drugs. In practice, this action is of value only in patients with severe hyperthyroidism or thyrotoxic crisis, and carbimazole and methimazole offer the advantages that fewer tablets are needed for initial treatment and that once-daily doses are effective at the start of treatment in patients with mild hyperthyroidism and after the first three to four weeks of treatment in those with more severe hyperthyroidism. Drug selection is largely determined by local practice. For instance, propylthiouracil is the drug of choice in North America, carbimazole in the United Kingdom, and methimazole elsewhere in Europe and in Asia.

Approximately 30 to 40 percent of patients who are treated with an antithyroid drug remain euthyroid 10 years after the discontinuation of antithyroid drug therapy, which means that the Graves' disease has remitted. Whether the remission is entirely spontaneous or is due to amelioration of hyperthyroidism or to an immunomodulatory action of these drugs is unclear.[4] If hyperthyroidism recurs after treatment with an antithyroid drug, there is little chance that a second course of treatment will result in permanent remission.

Repeated attempts to predict the outcome after drug therapy is stopped have failed to identify reliable markers, although young patients and those with large goiters, ophthalmopathy, or high serum concentrations of thyrotropin-receptor antibody at the time of diagnosis are unlikely to have permanent remissions.[62] With respect to regimens of antithyroid drugs, prospective, randomized trials have established that prolonging treatment beyond 18 months confers no benefit when the titration regimen is used (Table 2),[63] whereas treatment for more than 6 months confers no benefit with the "block–replace" regimen.[64] I prefer the block–replace regimen because it involves fewer visits to the clinic and because euthyroidism seems easier to maintain. Thyroxine is added to the antithyroid drug in the block–replace regimen to avert hypothyroidism, but an additional role of thyroxine —

TABLE 2. TREATMENTS FOR GRAVES' HYPERTHYROIDISM.

TREATMENT	DOSE	ADVERSE EFFECTS
Antithyroid drugs (carbimazole or its metabolite methimazole, or propylthiouracil)	Dose decreased as euthyroidism is achieved (titration regimen), or given as a single fixed high dose (e.g., 30 mg of methimazole daily or 40 mg of carbimazole daily) together with thyroxine to prevent hypothyroidism ("block–replace" regimen)	Minor Rash, urticaria, arthralgia, fever, anorexia, nausea, abnormalities of taste and smell Major Agranulocytosis, thrombocytopenia, acute hepatic necrosis, cholestatic hepatitis, lupus-like syndrome, vasculitis, insulin–autoimmune syndrome
Radioactive iodine	Usually based on clinical assessment, but some centers calculate doses on the basis of uptake and turnover studies	Transient or permanent hypothyroidism, transient worsening of ophthalmopathy, radiation thyroiditis, hypoparathyroidism, overexposure of children to radiation, thyrotoxic crisis*
Subtotal thyroidectomy or near-total thyroidectomy		Hypothyroidism, anesthetic complications, hypoparathyroidism, recurrent laryngeal-nerve damage, hemorrhage, and laryngeal edema

*The urine of patients who are receiving this radioactive agent must be disposed of properly.

TABLE 3. TREATMENT OF GRAVES' OPHTHALMOPATHY.

Mild or moderate disease
  Maintenance of euthyroidism
  Cessation of smoking
  Avoidance of bright light and dust
  Sleeping with head raised
  Use of artificial tears
  Use of simple eye ointment at night
  Diuretic therapy
Severe disease*
  Glucocorticoids (e.g., 40 to 80 mg of prednisone daily, with the dose tapered over a period of at least 3 months, with or without initial intravenous pulses of methylprednisolone)
  Radiotherapy (e.g., 20 Gy, given in 10 fractions of 2 Gy each)
  Surgical decompression of the orbits
  Experimental treatments, including immunosuppressive drugs (azathioprine or cyclosporine), usually given with glucocorticoids; intravenous immune globulin; octreotide; and plasma exchange
Stable disease
  Surgery on extraocular muscles to correct diplopia
  Cosmetic surgery to repair retraction of eyelids
  Orbital decompression to correct exophthalmos

*Severe disease is characterized by worsening diplopia, exposure keratitis, or optic neuropathy.

namely, to suppress the secretion of thyrotropin and thereby possibly prevent the release of thyroid antigens — was suggested by the finding of a very low rate of recurrent hyperthyroidism in one study of patients given thyroxine during and after a course of methimazole.[65] These results were not reproduced in several other studies for reasons that are unclear.[66]

The most serious complication of treatment with antithyroid drugs is agranulocytosis, with a probable frequency of less than 3 cases per 10,000 patient-years,[67] although some estimates are 10 times as high. Patients must be advised to stop the drug and have a white-cell count performed if a sore throat, fever, or mouth ulcers develop. Most physicians do not obtain routine white-cell counts, although one study in Japan suggested that if such tests were routine, granulocytopenia could be detected before symptoms occurred.[68] Treatment of agranulocytosis consists of discontinuation of the drug, hospitalization for monitoring, and treatment with a broad-spectrum antibiotic. A randomized trial of granulocyte colony-stimulating factor found no benefit.[69] A rarer serious complication is hepatotoxic effects (acute hepatic necrosis or cholestatic hepatitis), which can continue despite the discontinuation of drug therapy and may be fatal.[70]

Therapy with Radioactive Iodine

Radioactive iodine is the preferred initial treatment for patients with Graves' hyperthyroidism in North America.[71] In one analysis, it was the most cost-effective treatment,[72] but in another analysis the costs of treatment with an antithyroid drug were slightly less, with similar rates of acceptability to patients.[73] Radioactive iodine is contraindicated in pregnant women and those who are breast-feeding, and it can induce or worsen ophthalmopathy, particularly in smokers.[74,75] The worsening of ophthalmopathy is often transient

and may be prevented by glucocorticoid therapy (40 mg of prednisone daily, with the dose tapered to zero over a period of three months).[74] There is no established teratogenic risk of radioactive iodine, but conception should be deferred for at least four months after treatment. The relative advantages and disadvantages of radioactive iodine and antithyroid drugs are given in Table 4. I recommend an antithyroid drug for patients with a first episode of Graves' hyperthyroidism who are younger than 50 years of age, and radioactive iodine for those who are 50 years of age or older, because recurrent hyperthyroidism carries a risk of atrial fibrillation in this age group, and for any patient with recurrent hyperthyroidism, unless there is an indication for surgery.

Standardized mortality rates after radioactive iodine treatment in patients with all forms of hyperthyroidism are slightly increased, primarily as a result of hyperthyroidism, cardiovascular disease, and fractures of the femur.[76,77] The rates decline with time after treatment, and therefore they are most likely the result of the hyperthyroidism itself rather than due to a direct effect of treatment. The total incidence of cancer is either unchanged[78] or reduced[79] in patients who are treated with radioactive iodine, but the risk of death from thyroid cancer and possibly other cancers is slightly increased. Whether this risk is related to Graves' disease or radioactive iodine is not known. These reassuring data nonetheless suggest the need for caution in the treatment of children with Graves' hyperthyroidism.[80]

The main side effect of radioactive iodine is hypothyroidism. It may be transient when it occurs in the first few months after the administration of radioactive iodine: patients with the highest serum concentrations of thyroid-stimulating antibodies are the most likely to recover,[81] and some require a second treatment to cure their hyperthyroidism.[82] Elaborate calculation of the dose of radioactive iodine does not decrease the rates of hypothyroidism or recurrent hyperthyroidism, and it is expensive and inconvenient.[83] Most physicians prefer to give fixed doses of 5 to 15

TABLE 4. FACTORS RELEVANT TO THE CHOICE OF TREATMENT FOR PATIENTS WITH NEWLY DIAGNOSED GRAVES' HYPERTHYROIDISM.

FACTOR	ANTITHYROID DRUGS	RADIOACTIVE IODINE
Usual time to initial improvement	2 to 4 weeks in more than 90 percent of patients	4 to 8 weeks in 70 percent of patients
Likelihood of recurrence after treatment	60 to 70 percent	5 to 20 percent*
Likelihood of hypothyroidism	10 to 15 percent 15 years after treatment	10 to 30 percent during first 2 years after treatment; 5 percent per year thereafter*
Likelihood of other adverse effects†	Minor adverse effects in 5 percent of patients	Less than 1 percent
	Major adverse effects in less than 1 percent of patients	
Pregnancy or breast-feeding	Propylthiouracil in a titration regimen	Contraindicated
Planning pregnancy	Propylthiouracil in a titration regimen	Pregnancy should be avoided for at least 4 months after treatment
Concurrent severe ophthalmopathy	No adverse effects	May worsen after treatment, especially in smokers; can be prevented with prophylactic glucocorticoids
Very large goiter	High likelihood of recurrence	Requires larger dose to reduce the risk of recurrence
Childhood	Long-term treatment is often necessary	Theoretical risk of thyroid cancer
Requirement for repeated thyroid-function testing (e.g., if patient travels extensively)	"Block–replace" regimen usually maintains euthyroidism for an extended period	Regular assessment required because, in the year after treatment is initiated, thyroid function may vary
Interference with daily activities	None	Close contact with children and pregnant women must be avoided after treatment; time depends on local radiation protocols‡

*The risk depends on the dose of radioactive iodine that was administered.

†Other adverse effects are listed in Table 2.

‡The length of time varies depending on the dose of radioactive iodine that was administered.

mCi (185 to 555 MBq) on the basis of an assessment of the size of the thyroid.[84]

The administration of antithyroid drugs immediately before or after radioactive iodine reduces its effectiveness. This is a particular problem with propylthiouracil, which can have a radioprotective effect for up to 55 days.[85] Patients with mild or moderate hyperthyroidism do not require treatment with an antithyroid drug before or after radioactive iodine therapy; their symptoms can be adequately ameliorated with a beta-adrenergic antagonist until the radioactive iodine takes effect. Patients with severe hyperthyroidism should be treated with an antithyroid drug for four to eight weeks before radioactive iodine is given because the drug reduces thyroid secretion rapidly and thereby reduces the slight risk of the development of a thyrotoxic crisis soon after radioactive iodine administration. An antithyroid drug should be given after radioactive iodine therapy only in patients whose hyperthyroidism is poorly controlled at the time of the administration of radioactive iodine.

Thyroidectomy

Subtotal thyroidectomy is preferred by some patients with Graves' hyperthyroidism, especially those with a large goiter, and it may be indicated in patients with a coexistent thyroid nodule whose nature is unclear. The patient should be treated with an antithyroid drug until euthyroidism is achieved; inorganic iodide is also usually administered for seven days before surgery. Surgery is more costly than therapy with an antithyroid drug or radioactive iodine.[73] In the centers with the most experience, hyperthyroidism is cured in more than 98 percent of patients, with low rates of operative complications. The rate of postoperative hypothyroidism is higher when near-total thyroidectomy is performed than with subtotal thyroidectomy, and it is higher in patients with high serum thyroid peroxidase antibody concentrations.[86] Near-total thyroidectomy has no effect on ophthalmopathy.[87]

Graves' Disease in Pregnancy

Ideally, women with Graves' hyperthyroidism should avoid pregnancy until their hyperthyroidism is adequately treated, because the rate of fetal loss in untreated women is high. When Graves' hyperthyroidism occurs or recurs during pregnancy, an antithyroid drug should be given in the lowest dose necessary to maintain the woman's serum free thyroxine concentration in the upper part of the normal reference range or just above this range.[88] Combination therapy with an antithyroid drug and thyroxine must be avoided because the dose of antithyroid drug needs to be higher in patients who are also receiving thyroxine therapy, and little of the thyroxine reaches the fetus, resulting in fetal hypothyroidism. There is little difference between propylthiouracil and methimazole in terms of the potential of causing fetal hypothyroidism, despite the theoretically lower risk of transplacental transfer of propylthiouracil as a result of higher levels of drug binding to serum proteins.[89] Properly monitored treatment with an antithyroid drug is safe in pregnant women. There is a weak association between aplasia cutis congenita and maternal use of methimazole or carbimazole during pregnancy. The risk is uncertain, but studies to assess the frequency of this complication have had insufficient power to establish that no risk exists.[90] Since propylthiouracil is equally effective and has not been suspected of having teratogenic effects, it is usually used in pregnant women with hyperthyroidism.[88]

For unknown reasons, serum concentrations of thyroid-stimulating antibody decline and thyrotropin-receptor–blocking antibodies sometimes appear during pregnancy.[91] As a result, there is often spontaneous remission of hyperthyroidism in the last trimester of pregnancy, in which case therapy with antithyroid drugs can be stopped. Hyperthyroidism is present in the fetuses and neonates of 1 to 5 percent of women who have Graves' disease during pregnancy. It is caused by the transplacental passage of thyroid-stimulating antibodies; nearly all mothers of affected fetuses and neonates have very high serum concentrations of thyrotropin-receptor antibody. The risk of neonatal hyperthyroidism can be assessed by measuring maternal serum thyrotropin-receptor antibodies at the beginning of the third trimester; this test is particularly useful in women who are still taking an antithyroid drug at this time.[48,92] In fetuses, hyperthyroidism causes poor intrauterine growth and a heart rate of more than 160 beats per minute. In neonates, the symptoms and signs include tachycardia, hyperactivity, irritability, and weakness. Mothers who are taking low doses of any antithyroid drug may breastfeed safely, but the baby's thyroid status should be evaluated periodically.

Graves' Ophthalmopathy

Mild-to-moderate ophthalmopathy often improves spontaneously, and only simple measures are needed (Table 3). Severe ophthalmopathy, in particular impaired vision, improves in about two thirds of patients who are treated with high doses of glucocorticoids, orbital irradiation, or both.[93] Orbital decompression is effective in patients with optic neuropathy and exophthalmos, either as the initial treatment or after the failure of glucocorticoid treatment.[94] The place of other medical treatments is unclear.

CONCLUSIONS

By stimulating the thyrotropin receptor, antibodies have a crucial pathogenic role in Graves' disease. Genetic and environmental factors interact through unknown mechanisms to increase the risk of Graves' disease. The frequent association of ophthalmopathy with hyperthyroidism suggests a common autoimmune re-

sponse, which may be the result of the expression of thyrotropin in the orbits. Current treatments for Graves' hyperthyroidism are effective, but often at the expense of iatrogenic hypothyroidism, whereas the treatment of ophthalmopathy remains unsatisfactory. Further understanding of the immunologic processes involved should allow the development of better diagnostic methods and treatments.

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