TSH-secreting pituitary tumor, there is also a diffuse goiter. The presence of a nonsuppressed TSH level and the finding of a pituitary tumor on CT or magnetic resonance scan (MRI) scan suggest this diagnosis.

Clinical features of thyrotoxicosis can mimic certain aspects of other disorders, including panic attacks, mania, pheochromocytoma, and weight loss associated with malignancy. The diagnosis of thyrotoxicosis can be easily excluded if the TSH and unbound T_4 and T_3 levels are normal. A normal TSH also excludes Graves' disease as a cause of diffuse goiter.

Clinical Course Clinical features generally worsen without treatment; mortality was 10–30% before the introduction of satisfactory therapy. Some patients with mild Graves' disease experience spontaneous relapses and remissions. Rarely, there may be fluctuation between hypo- and hyperthyroidism due to changes in the functional activity of TSH-R antibodies. About 15% of patients who enter remission after treatment develop hypothyroidism 10–15 years later as a result of the destructive autoimmune process.

The clinical course of ophthalmopathy does not follow that of the thyroid disease. Ophthalmopathy typically worsens over the initial 3–6 months, followed by a plateau phase over the next 12–18 months, with spontaneous improvement, particularly in the soft tissue changes. However, the course is more fulminant in up to 5% of patients, requiring intervention in the acute phase if there is optic nerve compression or corneal ulceration. Diplopia may appear late in the disease due to fibrosis of the extraocular muscles. Radioiodine treatment for hyperthyroidism worsens the eye disease in a small proportion of patients (especially smokers). Antithyroid drugs or surgery have no adverse effects on the clinical course of ophthalmopathy. Thyroid dermopathy, when it occurs, usually appears 1–2 years after the development of Graves' hyperthyroidism; it may improve spontaneously.

TREATMENT GRAVES' DISEASE

The *hyperthyroidism* of Graves' disease is treated by reducing thyroid hormone synthesis, using antithyroid drugs, or reducing the amount of thyroid tissue with radioiodine (^{131}I) treatment or by thyroidectomy. Antithyroid drugs are the predominant therapy in many centers in Europe and Japan, whereas radioiodine is more often the first line of treatment in North America. These differences reflect the fact that no single approach is optimal and that patients may require multiple treatments to achieve remission.

The main *antithyroid drugs* are the thionamides, such as propylthiouracil, carbimazole (not available in the United States), and the active metabolite of the latter, methimazole. All inhibit the function of TPO, reducing oxidation and organification of iodide. These drugs also reduce thyroid antibody levels by mechanisms that remain unclear, and they appear to enhance rates of remission. Propylthiouracil inhibits deiodination of $T_4 \rightarrow T_3$. However, this effect is of minor benefit, except in the most severe thyrotoxicosis, and is offset by the much shorter half-life of this drug (90 min) compared to methimazole (6 h). Due to the hepatotoxicity of propylthiouracil, the U.S. Food and Drug Administration (FDA) has limited indications for its use to the first trimester of pregnancy, the treatment of thyroid storm, and patients with minor adverse reactions to methimazole. If propylthiouracil is used, monitoring of liver function tests is recommended.

There are many variations of antithyroid drug regimens. The initial dose of carbimazole or methimazole is usually 10–20 mg every 8 or 12 h, but once-daily dosing is possible after euthyroidism is restored. Propylthiouracil is given at a dose of 100–200 mg every 6–8 h, and divided doses are usually given throughout the course. Lower doses of each drug may suffice in areas of low iodine intake. The starting dose of antithyroid drugs can be gradually reduced (titration regimen) as thyrotoxicosis improves. Alternatively, high doses may be given combined with levothyroxine supplementation (block-replace regimen) to avoid drug-induced hypothyroidism. The titration regimen is preferred to minimize the dose of antithyroid drug and provide an index of treatment response.

Thyroid function tests and clinical manifestations are reviewed 4–6 weeks after starting treatment, and the dose is titrated based on unbound T_4 levels. Most patients do not achieve euthyroidism until 6–8 weeks after treatment is initiated. TSH levels often remain suppressed for several months and therefore do not provide a sensitive index of treatment response. The usual daily maintenance doses of antithyroid drugs in the titration regimen are 2.5–10 mg of carbimazole or methimazole and 50–100 mg of propylthiouracil. In the block-replace regimen, the initial dose of antithyroid drug is held constant, and the dose of levothyroxine is adjusted to maintain normal unbound T_4 levels. When TSH suppression is alleviated, TSH levels can also be used to monitor therapy.

Maximum remission rates (up to 30–60% in some populations) are achieved by 12–18 months for the titration regimen and by 6 months for the block-replace regimen. For unclear reasons, remission rates appear to vary in different geographic regions. Younger patients, males, smokers, and patients with severe hyperthyroidism and large goiters are most likely to relapse when treatment stops, but outcomes are difficult to predict. All patients should be followed closely for relapse during the first year after treatment and at least annually thereafter.

The common minor side effects of antithyroid drugs are rash, urticaria, fever, and arthralgia (1–5% of patients). These may resolve spontaneously or after substituting an alternative antithyroid drug. Rare but major side effects include hepatitis (propylthiouracil; avoid use in children) and cholestasis (methimazole and carbimazole); an SLE-like syndrome; and, most important, agranulocytosis (<1%). It is essential that antithyroid drugs are stopped and not restarted if a patient develops major side effects. Written instructions should be provided regarding the symptoms of possible agranulocytosis (e.g., sore throat, fever, mouth ulcers) and the need to stop treatment pending an urgent complete blood count to confirm that agranulocytosis is not present. Management of agranulocytosis is described in **Chap. 130**. It is not useful to monitor blood counts prospectively, because the onset of agranulocytosis is idiosyncratic and abrupt.

Propranolol (20–40 mg every 6 h) or longer-acting selective β_1 receptor blockers such as atenolol may be helpful to control adrenergic symptoms, especially in the early stages before antithyroid drugs take effect. Beta blockers are also useful in patients with thyrotoxic periodic paralysis, pending correction of thyrotoxicosis. In consultation with a cardiologist, anticoagulation with warfarin should be considered in all patients with atrial fibrillation who often spontaneously revert to sinus rhythm with control of hyperthyroidism. Decreased warfarin doses are required when patients are thyrotoxic. If digoxin is used, increased doses are often needed in the thyrotoxic state.

Radioiodine causes progressive destruction of thyroid cells and can be used as initial treatment or for relapses after a trial of antithyroid drugs. There is a small risk of thyrotoxic crisis (see below) after radioiodine, which can be minimized by pretreatment with antithyroid drugs for at least a month before treatment. Antecedent treatment with antithyroid drugs should be considered for all elderly patients or for those with cardiac problems to deplete thyroid hormone stores before administration of radioiodine. Carbimazole or methimazole must be stopped 3–5 days before radioiodine administration to achieve optimum iodine uptake. Propylthiouracil appears to have a prolonged radioprotective effect and should be stopped for a longer period before radioiodine is given, or a larger dose of radioiodine will be necessary.

Efforts to calculate an optimal dose of radioiodine that achieves euthyroidism without a high incidence of relapse or progression to hypothyroidism have not been successful. Some patients inevitably relapse after a single dose because the biologic effects of radiation vary between individuals, and hypothyroidism cannot be uniformly avoided even using accurate dosimetry. A practical strategy is to give a fixed dose based on clinical features, such as the severity of thyrotoxicosis, the size of the goiter (increases the dose needed), and the level of radioiodine uptake (decreases the dose needed). ^{131}I dosage generally ranges between 370 MBq (10 mCi) and 555 MBq