predominantly from increased circulating levels of T_3 ("T_3 toxicosis"). In these cases, free T_4 levels may be decreased, and direct measurement of serum T_3 may be useful. In rare cases of pituitary-associated (secondary) hyperthyroidism, TSH levels are either normal or raised. Determining TSH levels after the injection of thyrotropin-releasing hormone (TRH stimulation test) is used in the evaluation of cases of suspected hyperthyroidism with equivocal changes in the baseline serum TSH level. A normal rise in TSH after administration of TRH excludes secondary hyperthyroidism. Once the diagnosis of thyrotoxicosis has been confirmed by a combination of TSH assays and free thyroid hormone levels, measurement of radioactive iodine uptake by the thyroid gland can help to determine the etiology. For example, there may be diffusely increased uptake in the whole gland (Graves disease), increased uptake in a solitary nodule (toxic adenoma), or decreased uptake (thyroiditis).

The therapeutic options for hyperthyroidism include several medications, each with a different mechanism of action. Typically, these include a β-blocker to control symptoms induced by increased adrenergic tone, a thionamide to block new hormone synthesis, an iodine solution to block the release of thyroid hormone, and agents that inhibit peripheral conversion of T_4 to T_3. Radioiodine, which is incorporated into thyroid tissues, resulting in ablation of thyroid function over a period of 6 to 18 weeks, may also be used.

Hypothyroidism

***Hypothyroidism* is a condition caused by a structural or functional derangement that interferes with the production of thyroid hormone.** Hypothyroidism is a fairly common disorder. By some estimates the population prevalence of overt hypothyroidism is 0.3%, while subclinical hypothyroidism can be found in greater than 4%. The prevalence increases with age, and it is nearly tenfold more common in women than in men. It can result from a defect anywhere in the hypothalamic-pituitary-thyroid axis. As in the case of hyperthyroidism, this disorder is divided into *primary* and *secondary* forms, depending on whether the hypothyroidism arises from an intrinsic abnormality in the thyroid itself, or occurs as a result of pituitary and hypothalamic disease (Table 24-4). Primary hypothyroidism accounts for the vast majority of cases, and may be accompanied by an enlargement in the size of the thyroid gland (goiter).

Primary hypothyroidism can be congenital, autoimmune, or iatrogenic.

***Congenital hypothyroidism.* Worldwide, congenital hypothyroidism is most often the result of *endemic iodine deficiency* in the diet** (see later). Other rare forms of congenital hypothyroidism include *inborn errors of thyroid metabolism (dyshormonogenetic goiter)*, wherein any one of the multiple steps leading to thyroid hormone synthesis may be defective, such as (1) iodide transport into thyrocytes, (2) "organification" of iodine (binding of iodine to tyrosine residues of the storage protein, thyroglobulin), and (3) iodotyrosine coupling to form hormonally active T_3 and T_4. In rare instances there may be complete absence of thyroid parenchyma *(thyroid agenesis)*, or the gland may be greatly reduced in size *(thyroid hypoplasia)* due to germline mutations in genes responsible for thyroid development (Table 24-4).

Table 24-4 Causes of Hypothyroidism

Primary
Genetic defects in thyroid development (*PAX8, FOXE1*, TSH receptor mutations) (rare)
Thyroid hormone resistance syndrome (*THRB* mutations) (rare)
Postablative
Surgery, radioiodine therapy, or external irradiation
Autoimmune hypothyroidism
Hashimoto thyroiditis*
Iodine deficiency*
Drugs (lithium, iodides, *p*-aminosalicylic acid)*
Congenital biosynthetic defect (dyshormonogenetic goiter) (rare) *
Secondary (Central)
Pituitary failure (rare)
Hypothalamic failure (rare)

*Associated with enlargement of thyroid ("goitrous hypothyroidism"). Hashimoto thyroiditis and postablative hypothyroidism account for the majority of cases of hypothyroidism in developed countries. *FOXE1*, forkhead box E1; *PAX8*, paired box 8; *THRB*, thyroid hormone receptor β.

***Autoimmune hypothyroidism.* Autoimmune hypothyroidism is the most common cause of hypothyroidism in iodine-sufficient areas of the world.** The vast majority of cases of autoimmune hypothyroidism are due to Hashimoto thyroiditis. Circulating autoantibodies, including *antimicrosomal*, *antithyroid peroxidase*, and *antithyroglobulin* antibodies, are found in this disorder, and the thyroid is typically enlarged (goitrous). Autoimmune hypothyroidism can occur in isolation or in conjunction with autoimmune polyendocrine syndrome (APS), types 1 and 2 (see discussion in "Adrenal Glands").

Iatrogenic hypothyroidism. This can be caused by either *surgical or radiation-induced ablation*. A large resection of the gland (total thyroidectomy) for the treatment of hyperthyroidism or a primary neoplasm can lead to hypothyroidism. The gland may also be ablated by radiation, whether in the form of radioiodine administered for the treatment of hyperthyroidism, or exogenous irradiation, such as external radiation therapy to the neck. *Drugs* given intentionally to decrease thyroid secretion (e.g., methimazole and propylthiouracil) can also cause acquired hypothyroidism, as can agents used to treat nonthyroid conditions (e.g., lithium, *p*-aminosalicylic acid).

Secondary (or central) hypothyroidism is caused by deficiencies of TSH or, far more uncommonly, TRH. Any of the causes of hypopituitarism (for example, pituitary tumor, postpartum pituitary necrosis, trauma, and nonpituitary tumors), or of hypothalamic damage from tumors, trauma, radiation therapy, or infiltrative diseases can cause central hypothyroidism.

Cretinism

***Cretinism* refers to hypothyroidism that develops in infancy or early childhood**. The term *cretin* was derived from the French *chrétien*, meaning "Christian" or