"Christlike," and was applied to these unfortunates because they were considered to be so mentally retarded as to be incapable of sinning. In the past this disorder occurred fairly commonly in regions of the world where dietary iodine deficiency is endemic, such as the Himalayas, inland China, Africa, and other mountainous areas. It is now much less prevalent as a result of the widespread supplementation of foods with iodine. On rare occasions, cretinism may also result from genetic defects that interfere with the biosynthesis of thyroid hormone (dyshormonogenetic goiter, see earlier).

Clinical features of cretinism include impaired development of the skeletal system and central nervous system, manifested by severe mental retardation, short stature, coarse facial features, a protruding tongue, and umbilical hernia. The severity of the mental impairment seems to be related to the time at which thyroid deficiency occurs in utero. Normally, maternal T_3 and T_4 cross the placenta and are critical for fetal brain development. If there is maternal thyroid deficiency before the development of the fetal thyroid gland, mental retardation is severe. In contrast, maternal thyroid hormone deficiency later in pregnancy, after the fetal thyroid has become functional, does not affect normal brain development.

Myxedema

The term *myxedema* is applied to hypothyroidism developing in the older child or adult. Myxedema was first linked with thyroid dysfunction in 1873 by Sir William Gull in an article addressing the development of a "cretinoid state" in adults. The clinical manifestations vary with the age of onset of the deficiency. Older children show signs and symptoms intermediate between those of the cretin and those of the adult with hypothyroidism. In the adult the condition appears insidiously and may take years before arousing clinical suspicion.

Myxedema is marked by a slowing of physical and mental activity. The initial symptoms include generalized fatigue, apathy, and mental sluggishness, which may mimic depression. Speech and intellectual functions are slowed. Patients with myxedema are listless, cold intolerant, and frequently overweight. Decreased sympathetic activity results in constipation and decreased sweating. The skin is cool and pale because of decreased blood flow. Reduced cardiac output probably contributes to shortness of breath and decreased exercise capacity, two frequent complaints. Thyroid hormones regulate the transcription of several sarcolemmal genes, such as calcium ATPases and the β adrenergic receptor, and lowered expression of these genes results in a decrease in cardiac output. In addition, hypothyroidism promotes an atherogenic profile—an increase in total cholesterol and low-density lipoprotein (LDL) levels—that probably contributes to the increased cardiovascular mortality in this disease. Histologically, there is an accumulation of matrix substances, such as glycosaminoglycans and hyaluronic acid, in skin, subcutaneous tissue, and a number of visceral sites. This results in nonpitting edema, a broadening and coarsening of facial features, enlargement of the tongue, and deepening of the voice.

Laboratory evaluation plays a vital role in the diagnosis of suspected hypothyroidism because of the nonspecific nature of symptoms. Patients with unexplained increases in body weight or hypercholesterolemia should be assessed for potential hypothyroidism. **Measurement of the serum TSH level is the most sensitive screening test for this disorder.** The TSH level is increased in primary hypothyroidism as a result of a loss of feedback inhibition of TRH and TSH production by the hypothalamus and pituitary, respectively. The TSH level is not increased in persons with hypothyroidism due to primary hypothalamic or pituitary disease. T_4 levels are decreased in individuals with hypothyroidism of any origin.

Thyroiditis

Thyroiditis, or inflammation of the thyroid gland, encompasses a diverse group of disorders characterized by some form of thyroid inflammation.

Although multiple entities exist under the diagnostic umbrella of "thyroiditis," this discussion focuses on the three most common and clinically significant subtypes: (1) Hashimoto thyroiditis, (2) granulomatous (de Quervain) thyroiditis, and (3) subacute lymphocytic thyroiditis.

Hashimoto Thyroiditis

Hashimoto thyroiditis is an autoimmune disease that results in destruction of the thyroid gland and gradual and progressive thyroid failure. It is the most common cause of hypothyroidism in areas of the world where iodine levels are sufficient. The name is derived from the 1912 report by Hashimoto describing patients with goiter and intense lymphocytic infiltration of the thyroid *(struma lymphomatosa)*. It is most prevalent between 45 and 65 years of age and is more common in women than in men, with a female predominance of 10:1 to 20:1. It can also occur in children and is a major cause of nonendemic goiter in the pediatric population.

Pathogenesis. **Hashimoto thyroiditis is caused by a breakdown in self-tolerance to thyroid autoantigens.** This is exemplified by the presence of circulating autoantibodies against thyroglobulin and thyroid peroxidase in the vast majority of Hashimoto patients. The inciting events have not been elucidated, but possibilities include abnormalities of regulatory T cells (Tregs), or exposure of normally sequestered thyroid antigens (Chapter 6). Similar to other autoimmune diseases, Hashimoto thyroiditis has a strong genetic component. Increased susceptibility to Hashimoto thyroiditis is associated with polymorphisms in immune regulation-associated genes, including *cytotoxic T lymphocyte-associated antigen-4 (CTLA4)* and *protein tyrosine phosphatase-22 (PTPN22)*, both of which code for regulators of T-cell responses. Susceptibility to other autoimmune diseases, such as type 1 diabetes (see later), is also associated with polymorphisms in both *CTLA4* and *PTPN22*.

Induction of thyroid autoimmunity is accompanied by a progressive depletion of thyroid epithelial cells by apoptosis and replacement of the thyroid parenchyma by mononuclear cell infiltration and fibrosis. Multiple immunologic mechanisms may contribute to thyroid cell death, including (Fig. 24-10):