systemic autoimmune IgG4-related disease, which is associated with fibrosis and tissue infiltration by plasma cells producing IgG4 (Chapter 6).

KEY CONCEPTS

Thyroiditis

- Hashimoto thyroiditis is the most common cause of hypothyroidism in regions where dietary iodine levels are sufficient.
- Hashimoto thyroiditis is an *autoimmune* thyroiditis characterized by progressive destruction of thyroid parenchyma, Hürthle cell change, and mononuclear (lymphoplasmacytic) infiltrates, with germinal centers and with or without extensive fibrosis.
- Subacute lymphocytic thyroiditis often occurs after a pregnancy (*postpartum thyroiditis*), typically is painless, and is characterized by lymphocytic inflammation in the thyroid. It is also a type of autoimmune thyroiditis.
- Granulomatous (de Quervain) thyroiditis is a self-limited disease, probably secondary to a viral infection, and is characterized by pain and the presence of a granulomatous inflammation in the thyroid.

Graves Disease

Graves disease is the most common cause of endogenous hyperthyroidism. Graves reported in 1835 his observations of a disease characterized by "violent and long continued palpitations in females" associated with enlargement of the thyroid gland. The disease is characterized by a *triad* of clinical findings:

- *Hyperthyroidism* associated with diffuse enlargement of the gland
- Infiltrative *ophthalmopathy* with resultant exophthalmos
- Localized, infiltrative *dermopathy*, sometimes called *pretibial myxedema*, which is present in a minority of patients

Graves disease has a peak incidence between 20 and 40 years of age. Women are affected as much as 10 times more frequently than men. This disorder is said to affect 1.5% to 2% of women in the United States.

Pathogenesis. **Graves disease is an autoimmune disorder characterized by the production of autoantibodies against multiple thyroid proteins, most importantly the TSH receptor.** A variety of antibodies that can either stimulate or block the TSH receptor are detected in the circulation. The most common antibody subtype, known as *thyroid-stimulating immunoglobulin* (TSI), is observed in approximately 90% of patients with Graves disease. In contrast to antibodies reactive with thyroglobulin and thyroid peroxidase, TSI is almost never observed in other autoimmune diseases of the thyroid. TSI binds to the TSH receptor and mimics its actions, stimulating adenyl cyclase and increasing the release of thyroid hormones. As stated, some patients also have TSH receptor *blocking antibodies* in the circulation, and in a minority of patients these may lead to hypothyroidism.

Graves disease (hyperthyroidism) and Hashimoto thyroiditis (hypothyroidism) represent two extremes of autoimmune thyroid disorders, and not surprisingly share many underlying features. For example, as with Hashimoto thyroiditis, genetic factors are important in the etiology of Graves disease. The concordance rate in monozygotic twins is 30% to 40%, compared with less than 5% among dizygotic twins, and like Hashimoto thyroiditis, genetic susceptibility is linked to polymorphisms in immune-function genes like *CTLA4* and *PTPN22* and the HLA-DR3 allele.

Autoimmunity also plays a role in the development of the *infiltrative ophthalmopathy* that is characteristic of Graves disease. In Graves ophthalmopathy, the protrusion of the eyeball (exopthalmos) is associated with increased volume of the retroorbital connective tissues and extraocular muscles, for several reasons. These include (1) marked infiltration of the retroorbital space by mononuclear cells, predominantly T cells; (2) inflammation with edema and swelling of extraocular muscles; (3) accumulation of extracellular matrix components, specifically hydrophilic glycosaminoglycans such as hyaluronic acid and chondroitin sulfate; and (4) increased numbers of adipocytes (fatty infiltration). These changes displace the eyeball forward and can interfere with the function of the extraocular muscles. Studies performed in animal models suggest that orbital preadipocyte fibroblasts, which express the TSH receptor, appear to stimulate the autoimmune reaction. Activated CD4+ helper T cells secrete cytokines that stimulate fibroblast proliferation and synthesis of extracellular matrix proteins (glycosaminoglycans), leading to progressive infiltration of the retroorbital space and ophthalmopathy.

MORPHOLOGY

The thyroid gland is usually symmetrically enlarged due to **diffuse hypertrophy and hyperplasia** of thyroid follicular epithelial cells (Fig. 24-13*A*). Increases in weight to over 80 gm are not uncommon. On cut section, the parenchyma has a soft, meaty appearance resembling muscle. Histologically, the follicular epithelial cells in untreated cases are tall and more crowded than usual. This crowding often results in the formation of small papillae, which project into the follicular lumen and encroach on the colloid, sometimes filling the follicles (Fig. 24-13*B*). Such papillae lack fibrovascular cores, in contrast to those of papillary carcinoma (see later). The colloid within the follicular lumen is pale, with scalloped margins. Lymphoid infiltrates, consisting predominantly of T cells, along with scattered B cells and mature plasma cells, are present throughout the interstitium. Germinal centers are common.

Preoperative therapy alters the morphology of the thyroid in Graves disease. Administration of iodine causes involution of the epithelium and the accumulation of colloid by blocking thyroglobulin secretion. Treatment with the antithyroid drug propylthiouracil exaggerates the epithelial hypertrophy and hyperplasia by stimulating TSH secretion.

Changes in extrathyroidal tissue include lymphoid hyperplasia, especially enlargement of the thymus in younger patients. The heart may be hypertrophied, and ischemic changes may be present, particularly in patients with preexisting coronary artery disease. In patients with ophthalmopathy, the tissues of the orbit are edematous because of the presence of hydrophilic