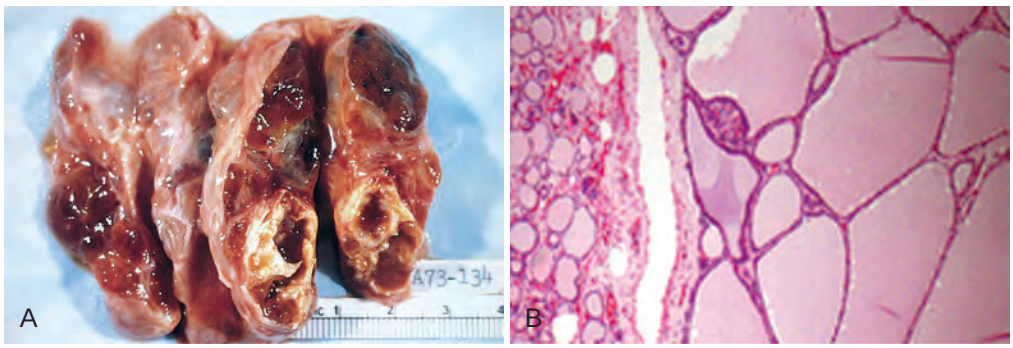

Figure 24-15 Multinodular goiter. **A,** Gross morphology demonstrating a coarsely nodular gland, containing areas of fibrosis and cystic change. **B,** Photomicrograph of a hyperplastic nodule, with compressed residual thyroid parenchyma on the periphery. Note absence of a prominent capsule, a distinguishing feature from follicular neoplasms. (**B,** Courtesy Dr. William Westra, Department of Pathology, Johns Hopkins University, Baltimore, Md.)

rise to adenomas, such cells can give rise to clones of proliferating cells. This may result in the formation of a nodule whose continued growth is autonomous, without the external stimulus. Consistent with this model, both polyclonal and monoclonal nodules coexist within the same multinodular goiter, the latter presumably having arisen because of the acquisition of a genetic abnormality favoring growth. Not surprisingly, activating mutations affecting proteins of the TSH-signaling pathway have been identified in a subset of autonomous thyroid nodules (TSH-signaling pathway mutations and their implications are discussed under "Adenomas"). The uneven follicular hyperplasia, generation of new follicles, and accumulation of colloid produce physical stress that may lead to rupture of follicles and vessels followed by hemorrhages, scarring, and sometimes calcifications. With scarring, nodularity appears, which may be accentuated by the preexisting stromal framework of the gland.

MORPHOLOGY

Multinodular goiters are multilobulated, asymmetrically enlarged glands that can reach weights of more than 2000 gm. The pattern of enlargement is quite unpredictable and may involve one lobe far more than the other, producing lateral pressure on midline structures, such as the trachea and esophagus. In other instances the goiter grows behind the sternum and clavicles to produce the so-called **intrathoracic** or **plunging goiter.** Occasionally, most of it is hidden behind the trachea and esophagus; in other instances one nodule may stand out, imparting the clinical appearance of a solitary nodule. On cut section, irregular nodules containing variable amounts of brown, gelatinous colloid are present (Fig. 24-15A). Older lesions have areas of hemorrhage, fibrosis, calcification, and cystic change. The microscopic appearance includes colloid-rich follicles lined by flattened, inactive epithelium and areas of **follicular hyperplasia**, accompanied by degenerative changes related to physical stress. In contrast to follicular neoplasms, a prominent capsule between the hyperplastic nodules and residual compressed thyroid parenchyma is not present (Fig. 24-15*B*).

Clinical Course. The dominant clinical features of multinodular goiter are those caused by *mass effects*. In addition to the obvious cosmetic effects, goiters may cause airway obstruction, dysphagia, and compression of large vessels in the neck and upper thorax *(superior vena cava syndrome)*. Most patients are euthyroid or have subclinical hyperthyroidism (identified only by reduced TSH levels), but in a substantial minority of patients an autonomous nodule may develop within a long-standing goiter and produce hyperthyroidism *(toxic multinodular goiter)*. This condition, known as *Plummer syndrome*, is not accompanied by the infiltrative ophthalmopathy and dermopathy of Graves disease. It is estimated that clinically apparent autonomous nodules develop in approximately 10% of multinodular goiters over a 10-year follow-up. The incidence of malignancy in long-standing multinodular goiters is low (<5%) but not zero, and concern for malignancy arises in goiters that demonstrate sudden changes in size or symptoms (e.g., hoarseness). Dominant nodules in a multinodular goiter can present as a "solitary thyroid nodule", mimicking a thyroid neoplasm. A radioiodine scan demonstrates uneven iodine uptake (including the occasional "hot" autonomous nodule) consistent with the diffuse parenchymal involvement, and an admixture of hyperplastic and involuting nodules. A fine-needle aspiration biopsy is helpful and can often, albeit not always, facilitate the distinction of follicular hyperplasia from a thyroid neoplasm (see later).

Neoplasms of the Thyroid

The solitary thyroid nodule is a palpably discrete swelling within an otherwise apparently normal thyroid gland. The estimated incidence of solitary palpable nodules in the adult population of the United States varies between 1% and 10%, but is significantly higher in endemic goitrous regions. Single nodules are about four times more common in women than in men. The incidence of thyroid nodules increases throughout life.

From a clinical standpoint, the major concern in persons who present with thyroid nodules is the possibility of a malignant neoplasm. Fortunately, the overwhelming majority of solitary nodules of the thyroid prove to be localized, nonneoplastic lesions (e.g., a dominant nodule in multinodular goiter, simple cysts, or foci of thyroiditis) or benign neoplasms such as follicular adenoma. In fact, *benign neoplasms outnumber thyroid carcinomas by a ratio of nearly 10:1*. While less than 1% of solitary thyroid nodules are malignant, this still represents about 15,000 new cases