of thyroid carcinoma per year in the United States. Fortunately, most of these cancers are indolent; more than 90% of affected patients are alive 20 years after being diagnosed.

Several clinical criteria provide clues to the nature of a thyroid nodule:

- *Solitary nodules,* in general, are more likely to be neoplastic than are multiple nodules.
- *Nodules in younger patients* are more likely to be neoplastic than are those in older patients.
- *Nodules in males* are more likely to be neoplastic than are those in females.
- A history of *radiation* treatment to the head and neck region is associated with an increased incidence of thyroid malignancy.
- Functional nodules that take up radioactive iodine in imaging studies *(hot nodules)* are much more likely to be benign than malignant.

These associations and statistics, however, are of little comfort to a patient, in whom the timely recognition of a malignancy can be lifesaving. Ultimately, morphologic evaluation of a given thyroid nodule, by fine-needle aspiration and surgical resection, provides the most definitive information about its nature. The following sections consider the major thyroid tumors, including adenoma and carcinoma in its various forms.

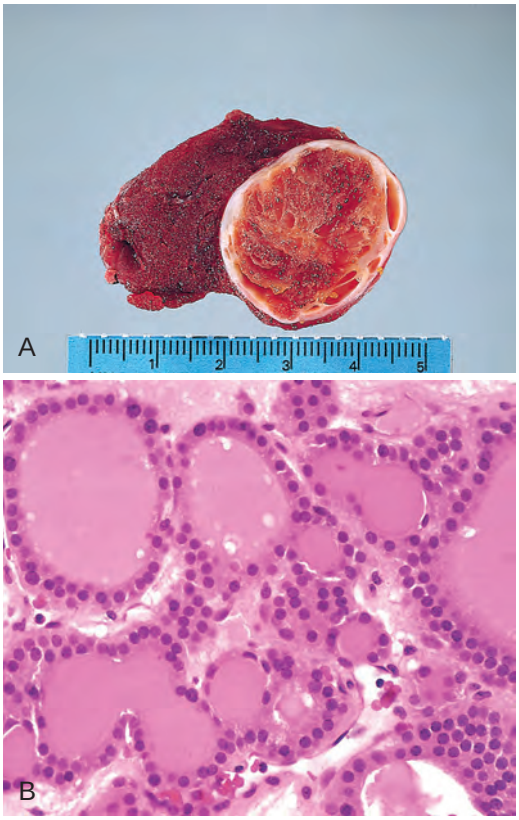

Figure 24-16 Follicular adenoma of the thyroid. **A,** A solitary, well-circumscribed nodule is seen. **B,** The photomicrograph shows well-differentiated follicles resembling normal thyroid parenchyma.

Adenomas

Adenomas of the thyroid are typically discrete, solitary masses, derived from follicular epithelium, and hence they are also known as *follicular adenomas*. Clinically, follicular adenomas can be difficult to distinguish from dominant nodules of follicular hyperplasia or from the less common follicular carcinomas. In general, follicular adenomas are *not* forerunners to carcinomas; nevertheless, shared genetic alterations support the possibility that at least of subset of follicular carcinomas arises in preexisting adenomas (see later). Although the vast majority of adenomas are nonfunctional, a small subset produces thyroid hormones and causes clinically apparent thyrotoxicosis. Hormone production in functional adenomas ("toxic adenomas") is independent of TSH stimulation.

***Pathogenesis.* Somatic mutations of the *TSH receptor signaling pathway* are found in toxic adenomas, as well as in toxic multinodular goiter.** Gain-of-function mutations in one of two components of this signaling system—most often the gene encoding the TSH receptor (TSHR) or the α-subunit of G_s (*GNAS*)—cause follicular cells to secrete thyroid hormone independent of TSH stimulation ("thyroid autonomy"). This leads to symptoms of hyperthyroidism and produces a functional "hot" nodule on imaging. Overall, mutations in the TSH receptor signaling pathway are present in slightly over half of toxic thyroid nodules. Notably, *TSHR* and *GNAS* mutations are rare in follicular carcinomas; thus, toxic adenomas and toxic multinodular goiter do not seem to be forerunners of malignancy.

A minority (<20%) of *nonfunctioning* follicular adenomas have mutations of *RAS or PIK3CA*, which encodes a subunit of the PI-3 kinase, or bear a *PAX8-PPARG* fusion gene, genetic alterations that are shared with follicular carcinomas. These are discussed in further detail under "Carcinomas" (see later).

MORPHOLOGY

The typical thyroid adenoma is a solitary, spherical, encapsulated lesion that is demarcated from the surrounding thyroid parenchyma by a well-defined, intact capsule (Fig. 24-16A). **These features are important in making the distinction from multinodular goiters,** which contain multiple nodules even in patients presenting clinically with a solitary dominant nodule. Follicular adenomas average about 3 cm in diameter, but some are much larger (≥10 cm in diameter). In freshly resected specimens the adenoma bulges from the cut surface and compresses the adjacent thyroid. The color ranges from gray-white to red-brown, depending on the cellularity of the adenoma and its colloid content. Areas of hemorrhage, fibrosis, calcification, and cystic change, similar to those encountered in multinodular goiters, are common in follicular adenomas, particularly within larger lesions.

Microscopically, the constituent cells often form uniform-appearing follicles that contain colloid (Fig. 24-16*B*). The follicular growth pattern is usually quite distinct from the adjacent nonneoplastic thyroid. The neoplastic cells show little variation in cell size, cell shape, or nuclear morphology, and mitotic figures are rare. Occasionally the neoplastic cells acquire brightly eosinophilic granular cytoplasm (*oxyphil* or *Hürthle cell change*) (Fig. 24-17). The hallmark of all follicular adenomas is