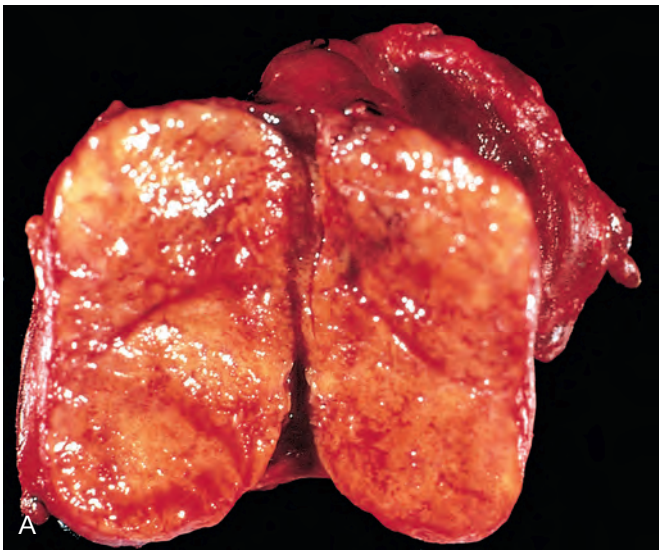
***Clinical Course.*** Anaplastic carcinomas usually present as a rapidly enlarging bulky neck mass. In most cases, the disease has already spread beyond the thyroid capsule into adjacent neck structures or has metastasized to the lungs at the time of presentation. Symptoms related to compression and invasion, such as dyspnea, dysphagia, hoarseness, and cough, are common. There are no effective therapies, and the disease is almost uniformly fatal. Although metastases to distant sites are common, in most cases death occurs in less than 1 year as a result of aggressive growth and compromise of vital structures in the neck.

### *Medullary Carcinoma*

**Medullary carcinomas of the thyroid are neuroendocrine neoplasms derived from the parafollicular cells, or C cells,** of the thyroid, and account for approximately 5% of thyroid neoplasms. Medullary carcinomas, similar to normal C cells, secrete *calcitonin*, the measurement of which plays an important role in the diagnosis and postoperative follow-up of patients. In some instances the tumor cells elaborate other polypeptide hormones, such as serotonin, ACTH, and vasoactive intestinal peptide (VIP). About 70% of tumors arise sporadically. The remainder occurs in the setting of MEN syndrome 2A or 2B or as familial tumors without an associated MEN syndrome (familial medullary thyroid carcinoma, or FMTC; see "Multiple Endocrine Neoplasia Syndromes"). Recall that *activating point mutations in the RET proto-oncogene* play an important role in the development of both familial and sporadic medullary carcinomas. Cases associated with MEN types 2A or 2B occur in younger patients, and may even arise during the first decade of life. In contrast, sporadic as well as familial medullary carcinomas are lesions of adulthood, with a peak incidence in the 40s and 50s.



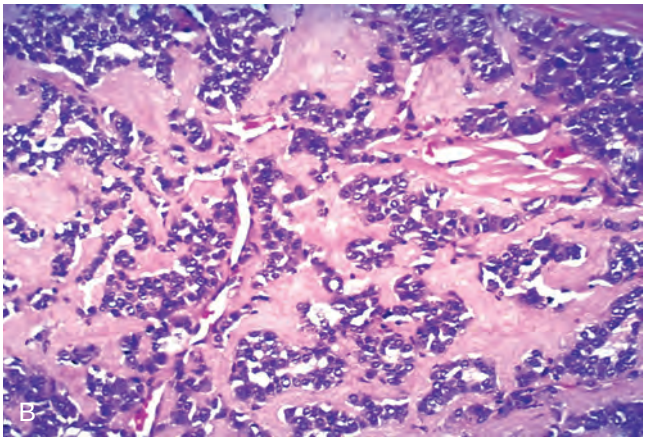




**Figure 24-22** Medullary carcinoma of thyroid. **A,** These tumors typically show a solid pattern of growth and do not have connective tissue capsules. **B,** Histology demonstrates abundant deposition of amyloid, visible here as homogeneous extracellular material, derived from calcitonin molecules secreted by the neoplastic cells. (**A,** Courtesy Dr. Joseph Corson, Brigham and Women's Hospital, Boston, Mass.)

## MORPHOLOGY

Sporadic medullary thyroid carcinomas present as a solitary nodule (Fig. 24-22*A*). In contrast, **bilaterality and multicentricity are common in familial cases**. Larger lesions often contain areas of necrosis and hemorrhage and may extend through the capsule of the thyroid. The tumor tissue is firm, pale gray to tan, and infiltrative. There may be foci of hemorrhage and necrosis in the larger lesions.

Microscopically, medullary carcinomas are composed of polygonal to spindle-shaped cells, which may form nests, trabeculae, and even follicles. Small, more anaplastic cells are present in some tumors and may be the predominant cell type. Acellular **amyloid deposits** derived from calcitonin polypeptides are present in the stroma in many cases (Fig. 24-22*B*). Calcitonin is readily demonstrable within the cytoplasm of the tumor cells as well as in the stromal amyloid by immunohistochemical methods. As with all neuroendocrine tumors, electron microscopy reveals variable numbers of membrane-bound electron-dense granules within the cytoplasm of the neoplastic cells (Fig. 24-23). One of the features of familial medullary cancers is the presence of multicentric **C-cell hyperplasia** in the surrounding thyroid parenchyma, a feature that is usually absent in sporadic lesions, and that is believed to be a precursor lesion in familial cases. Thus, the presence of multiple prominent clusters of C cells scattered throughout the parenchyma should raise the specter of an inherited predisposition, even if a family history is not present.

***Clinical Course.*** *Sporadic* cases of medullary carcinoma come to medical attention most often as a mass in the neck, sometimes associated with dysphagia or hoarseness. In some instances, the initial manifestations are those of a paraneoplastic syndrome caused by the secretion of a peptide hormone (e.g., diarrhea due to the secretion of VIP, or Cushing syndrome due to ACTH). Notably, hypocalcemia is not a prominent feature, despite the presence of raised calcitonin levels. In addition to circulating calcitonin, secretion of carcinoembryonic antigen by the neoplastic cells is a useful biomarker, especially for presurgical assessment of tumor load and in calcitonin-negative tumors.

Patients with *familial syndromes* may come to attention because of symptoms localized to the thyroid or as a result of endocrine neoplasms in other organs (e.g., adrenal or