some of which may antedate the development of a detectable pulmonary lesion. The hormones or hormone-like factors elaborated include:

- *Antidiuretic hormone* (ADH), inducing hyponatremia due to inappropriate ADH secretion
- *Adrenocorticotropic hormone* (ACTH), producing Cushing syndrome
- *Parathormone, parathyroid hormone-related peptide, prostaglandin E, and some cytokines*, all implicated in the hypercalcemia often seen with lung cancer
- *Calcitonin*, causing hypocalcemia
- *Gonadotropins*, causing gynecomastia
- *Serotonin and bradykinin*, associated with the carcinoid syndrome

The incidence of clinically significant syndromes related to these factors in lung cancer patients ranges from 1% to 10%, although a much higher proportion of patients show elevated serum levels of these (and other) peptide hormones. Any histologic type of tumor may occasionally produce any one of the hormones, but tumors that produce ACTH and ADH are predominantly small cell carcinomas, whereas those that produce hypercalcemia are mostly squamous cell carcinomas.

Other systemic manifestations of lung carcinoma include the *Lambert-Eaton myasthenic syndrome* (Chapter 26), in which muscle weakness is caused by auto-antibodies (possibly elicited by tumor ionic channels) directed to the neuronal calcium channel; *peripheral neuropathy*, usually purely sensory; dermatologic abnormalities, including *acanthosis nigricans* (Chapter 25); hematologic abnormalities, such as *leukemoid reactions,* hypercoagulable states such as *Trousseau syndrome* (deep vein thrombosis and thromboembolism); and finally, a peculiar abnormality of connective tissue called *hypertrophic pulmonary osteoarthropathy*, associated with clubbing of the fingers.

Apical lung cancers in the superior pulmonary sulcus tend to invade the neural structures around the trachea, including the cervical sympathetic plexus, and produce a group of clinical findings that includes severe pain in the distribution of the ulnar nerve and *Horner syndrome* (enophthalmos, ptosis, miosis, and anhidrosis) on the same side as the lesion. Such tumors are also referred to as *Pancoast tumors*.

## KEY CONCEPTS

### Carcinomas of the Lung

- The four major histologic subtypes are adenocarcinomas (most common), squamous cell carcinoma, large cell carcinoma, and small cell carcinoma.
- Each of these is clinically and genetically distinct. Small cell lung carcinomas are best treated by chemotherapy, because almost all are metastatic at presentation. The other carcinomas may be curable by surgery if limited to the lung. Combination chemotherapy also is available along with tyrosine kinase inhibitors for those with EGFR, ALK, ROS, and c-MET mutations.
- Smoking is the most important risk factor for lung cancer; in women and nonsmokers, adenocarcinomas are the most common cancers.
- Precursor lesions include squamous dysplasia for squamous cancer and atypical adenomatous hyperplasia and adenocarcinoma in situ (formerly bronchioloalveolar carcinoma) for adenocarcinomas.
- Tumors 3 cm or less in diameter characterized by pure growth along preexisting structures (lepidic pattern) without stromal invasion are now called *adenocarcinoma in situ*.
- Lung cancers, particularly small cell lung carcinomas, can cause paraneoplastic syndromes.

## Neuroendocrine Proliferations and Tumors

The normal lung contains neuroendocrine cells within the epithelium as single cells or as clusters, the neuroepithelial bodies. While virtually all pulmonary neuroendocrine cell hyperplasias are secondary to airway fibrosis and/or inflammation, a rare disorder called *diffuse idiopathic pulmonary neuroendocrine cell hyperplasia* seems to be a precursor to the development of multiple tumorlets and typical or atypical carcinoids.

Neoplasms of neuroendocrine cells in the lung include benign *tumorlets*, small, inconsequential, hyperplastic nests of neuroendocrine cells seen in areas of scarring or chronic inflammation; *carcinoids*; and the (already discussed) highly aggressive small cell carcinoma and large cell neuroendocrine carcinoma of the lung. Carcinoid tumors are classified separately, since they differ significantly from carcinomas with evidence of neuroendocrine differentiation in terms of incidence and clinical, epidemiologic, histologic, and molecular characteristics. For example, in contrast to small cell and large cell neuroendocrine carcinomas, carcinoids may occur in patients with multiple endocrine neoplasia type 1.

### Carcinoid Tumors

Carcinoid tumors represent 1% to 5% of all lung tumors. Most patients with these tumors are younger than 40 years of age, and the incidence is equal for both sexes. Approximately 20% to 40% of patients are nonsmokers. Carcinoid tumors are low-grade malignant epithelial neoplasms that are subclassified into *typical* and *atypical carcinoids*.

## MORPHOLOGY

Carcinoids may arise centrally or may be peripheral. On gross examination, the central tumors grow as fingerlike or spherical polypoid masses that commonly project into the lumen of the bronchus and are usually covered by an intact mucosa (Fig. 15-47*A*). They rarely exceed 3 to 4 cm in diameter. Most are confined to the mainstem bronchi. Others, however, penetrate the bronchial wall to fan out in the peribronchial tissue, producing the so-called **collar-button lesion**. Peripheral tumors are solid and nodular.

Histologically, the tumor is composed of organoid, trabecular, palisading, ribbon, or rosette-like arrangements of cells separated by a delicate fibrovascular stroma. In common with the lesions of the gastrointestinal tract, the individual cells are quite regular and have uniform round nuclei and a moderate