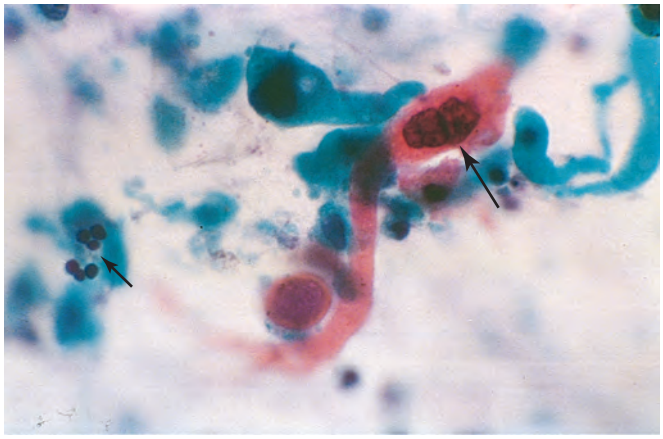

Figure 15-45 Cytologic diagnosis of lung cancer. A sputum specimen shows an orange-staining, keratinized squamous carcinoma cell with a prominent hyperchromatic nucleus *(large arrow)*. Note the size of the tumor cells compared with normal neutrophils (*small arrow*).

differentiated tumors, and are focally seen in poorly differentiated tumors. Mitotic activity is higher in poorly differentiated tumors. In the past, most squamous cell carcinomas were seen to arise centrally from the segmental or subsegmental bronchi. However, the incidence of squamous cell carcinoma of the peripheral lung is increasing. Squamous metaplasia, epithelial dysplasia, and foci of frank carcinoma in situ may be seen in bronchial epithelium adjacent to the tumor mass (Fig. 15-44).

Small cell carcinoma is a highly malignant tumor with a strong relationship to cigarette smoking; only about 1% occurs in nonsmokers. They may arise in major bronchi or in the periphery of the lung. There is no known preinvasive phase. They are the most aggressive of lung tumors, metastasizing widely and virtually always proving to be fatal.

Small cell carcinoma is comprised of relatively small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin (salt and pepper pattern), and absent or inconspicuous nucleoli (Fig. 15-43*C*). The cells are round, oval, or spindle-shaped, and nuclear molding is prominent. There is no absolute size for the tumor cells, but in general they are smaller than three

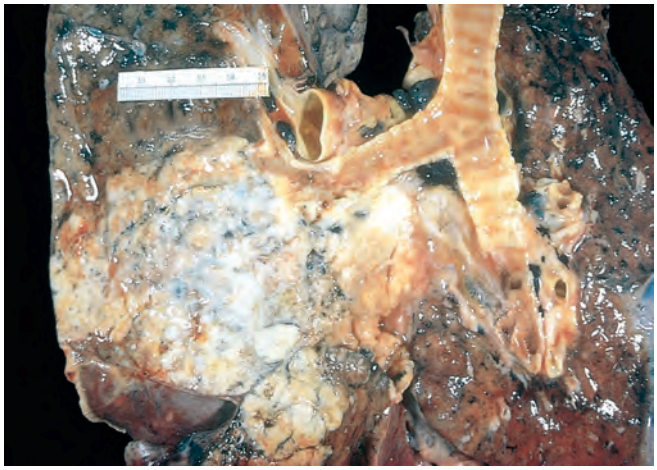

Figure 15-46 Lung carcinoma. The gray-white tumor infiltrates the lung parenchyma. Histologic sections identified this tumor as a squamous cell carcinoma.

times the diameter of a small resting lymphocyte (a size of about 25 microns). The mitotic count is high. The cells grow in clusters that exhibit neither glandular nor squamous organization. Necrosis is common and often extensive. Basophilic staining of vascular walls due to encrustation by DNA from necrotic tumor cells (Azzopardi effect) is frequently present. All small cell carcinomas are high grade. Combined small cell carcinoma is a variant in which typical small cell carcinoma is mixed with non-small cell histologies, such as large cell neuroendocrine carcinoma and even spindled cell morphologies resembling sarcoma.

Electron microscopy shows dense-core neurosecretory granules, about 100 nm in diameter, in two thirds of cases. The occurrence of neurosecretory granules, the expression of neuroendocrine markers such as chromogranin, synaptophysin, and CD57, and the ability of some of these tumors to secrete hormones (e.g., parathormone-related protein, a cause of paraneoplastic hypercalcemia) suggest that this tumor originates from neuroendocrine progenitor cells, which are present in the lining bronchial epithelium. Among the various types of lung cancer, small cell carcinoma is the one that is most commonly associated with ectopic hormone production (discussed later). Immunohistochemistry demonstrates high levels of the anti-apoptotic protein BCL2 in 90% of tumors.

Large cell carcinoma is an undifferentiated malignant epithelial tumor that lacks the cytologic features of other forms of lung cancer. The cells typically have large nuclei, prominent nucleoli, and a moderate amount of cytoplasm (Fig. 15-43*D*). Large cell carcinoma is a diagnosis of exclusion since is expresses none of the markers associated with adenocarcinoma (TTF-1, napsin A) and squamous cell carcinoma (p63, p40) (Fig 15-43*A* inset). One histologic variant is large cell neuroendocrine carcinoma, which has molecular features similar to those that characterize small cell carcinoma, but is comprised of tumor cells of larger size.

Any type of lung carcinoma may extend on to the pleural surface and then within the pleural cavity or into the pericardium. Metastases to the bronchial, tracheal, and mediastinal nodes can be found in most cases. The frequency of nodal involvement varies slightly with the histologic pattern but averages greater than 50%.

Distant spread of lung carcinoma occurs through both lymphatic and hematogenous pathways. These tumors often spread early throughout the body except for squamous cell carcinoma, which metastasizes outside the thorax late. Metastasis may be the first manifestation of an underlying occult pulmonary lesion. No organ or tissue is spared in the spread of these lesions, but the adrenals, for obscure reasons, are involved in more than half the cases. The liver (30% to 50%), brain (20%), and bone (20%) are additional favored sites of metastases.

Combined Carcinoma. Approximately 10% of all lung carcinomas have a combined histology, including two or more of the aforementioned types.

Secondary Pathology. Lung carcinomas have local effects that may cause several pathologic changes in the lung distal to the point of bronchial involvement. Partial obstruction may cause marked **focal emphysema;** total obstruction may lead to **atelectasis.** The impaired drainage of the airways is a common cause for **severe suppurative or ulcerative bronchitis** or **bronchiectasis. Pulmonary abscesses** sometimes call attention to an otherwise silent carcinoma. Compression or invasion of the superior vena cava can cause venous