dehiscence, vascular thrombosis, primary graft dysfunction) are becoming rare. The transplanted lung is subject to two major complications: infection and rejection.

- *Pulmonary infections* in lung transplant patients are essentially those of any immunocompromised host, discussed earlier. In the early posttransplant period (the first few weeks), bacterial infections are most common. With ganciclovir prophylaxis and matching of donor-recipient CMV status, CMV pneumonia occurs less frequently and is less severe, although some resistant strains are emerging. Most infections occur in the third to twelfth month after transplantation. *P. jiroveci* pneumonia is rare, since almost all patients receive adequate prophylaxis, usually with trimethoprim-sulfamethoxazole (Bactrim). Fungal infections are mostly due to *Aspergillus* and *Candida* species, and they may involve the bronchial anastomotic site and/or the lung.
- *Acute lung allograft rejection* occurs to some degree in all patients despite routine immunosuppression. It most often appears several weeks to months after surgery but also may present years later or whenever immunosuppression is decreased. Patients present with fever, dyspnea, cough, and radiologic infiltrates. Since these are similar to the picture of infections, diagnosis often relies on transbronchial biopsy.
- *Chronic lung allograft rejection* is a significant problem in at least half of all patients by 3 to 5 years posttransplant. It is manifested by cough, dyspnea, and an irreversible decrease in lung function due to pulmonary fibrosis.

MORPHOLOGY

The morphologic features of acute rejection are primarily those of inflammatory infiltrates (lymphocytes, plasma cells, and few neutrophils and eosinophils) around small vessels, in the submucosa of airways, or both. The major morphologic correlate of chronic rejection is **bronchiolitis obliterans,** the partial or complete occlusion of small airways by fibrosis, with or without active inflammation (Fig. 15.40). Bronchiolitis obliterans is patchy and therefore difficult to diagnose via transbronchial biopsy. Bronchiectasis and pulmonary fibrosis may also develop with long-standing chronic rejection.

Acute cellular airway rejection (the presumed forerunner of later, fibrous obliteration of these airways) is generally responsive to therapy, but the treatment of established bronchiolitis obliterans has been disappointing. Its progress may be slowed or even halted for some time, but it cannot be reversed. Infrequent complications of lung transplantation include Epstein-Barr virus (EBV)–associated B-cell lymphoma, which most often arises within the lung allograft. With continuing improvement in surgical, immunosuppressive, and antimicrobial therapies, the outcome of lung transplantation has improved considerably. The overall median survival is 6 years, with younger patients and those undergoing bilateral lung transplantation having better outcomes.

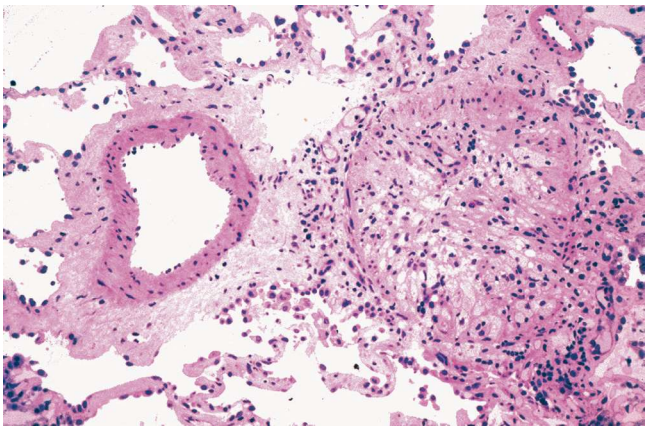

Figure 15.40 Chronic rejection of lung allograft associated with bronchiole (bronchiolitis obliterans). An adjacent pulmonary artery is normal. (Courtesy Dr. Thomas Krausz, Department of Pathology, The University of Chicago, Pritzker School of Medicine, Chicago, Ill.)

TUMORS

Of the wide variety of benign and malignant tumors that may arise in the lung, 90% to 95% are carcinomas, about 5% are carcinoid tumors, and 2% to 5% are mesenchymal and other miscellaneous neoplasms.

Carcinomas

Lung cancer is currently the most frequently diagnosed major cancer and the most common cause of cancer mortality worldwide. Globally, in 2018 there were an estimated 2.1 million new cases and 1.8 million lung cancer deaths. The number of new cases of lung cancer in 2018 in the United States is expected to number approximately 230,000 (note that in 1950 it was 18,000), accounting for about 14% of cancer diagnoses and taking more than 150,000 lives, which amounts to roughly 28% of all cancer-related deaths. Each year, lung cancer kills more people than colon, breast, and prostate cancer combined. It is generally a disease of older adults, occurring most often between ages 55 and 84 years, with a peak incidence between 65 and 74 years. Only 2% of all cases occur before the age of 40.

Because lung cancer is strongly linked to cigarette smoking, changes in smoking habits greatly influence lung cancer incidence and mortality as well as the prevalence of the various histologic types of lung cancer. Since the early 1990s, lung cancer incidence and mortality rates have been decreasing in men due to a decrease in male smoking over the past 35 years. However, the decrease in smoking among women has lagged behind that of men. Since 1987 more women have died each year of lung cancer than of breast cancer, which for more than 40 years had been the leading cause of cancer death in women.

Etiology and Pathogenesis

Most (but not all) lung cancers are associated with a well-known carcinogen—cigarette smoke. In addition, there are other genetic and environmental factors. Lung cancers are

broadly classified into small cell and non–small cell types, with the latter group including adenocarcinoma and squamous cell carcinoma. The driver mutations that cause lung cancer vary among these histologic subtypes, as will be described later.

Tobacco Smoking. **About 80% of lung cancers occur in active smokers or those who stopped recently, and there is a nearly linear correlation between the frequency of lung cancer and pack-years of cigarette smoking.** The increased risk is 60 times greater in habitual heavy smokers (two packs a day for 20 years) than in nonsmokers. However, since lung cancer develops in only 10% to 15% of smokers, there are likely to be other factors that interact with smoking to predispose individuals to this deadly disease. For unclear reasons, it appears that women are more susceptible to carcinogens in tobacco than men. Although cessation of smoking decreases the risk for lung cancer over time, it may never return to baseline levels. In fact, genetic changes that predate lung cancer can persist for many years in the bronchial epithelium of former smokers. Pipe and cigar smokers also incur an elevated risk, albeit only modestly. Chewing tobacco is not a safe substitute for smoking cigarettes or cigars, as these products spare the lung but cause oral cancers and can lead to nicotine addiction. The long-term effects of electronic cigarette aerosols are not known, as "vaping" is a relatively recent phenomenon (Chapter 9).

Unfortunately, the carcinogenic effects of tobacco smoke extend to those who live and work with smokers. *Secondhand smoke,* or environmental tobacco smoke, contains numerous human carcinogens for which there is no safe level of exposure. It is estimated that each year about 3000 nonsmoking adults die of lung cancer as a result of breathing secondhand smoke.

What of heavy smokers who never develop cancer? While some of this may be a matter of chance, the mutagenic effect of carcinogens in smoke is modified by genetic variants. Recall that many chemicals (procarcinogens) are converted into carcinogens via activation by the highly polymorphic P-450 monooxygenase enzyme system (Chapter 9). Specific P-450 variants have an increased capacity to activate procarcinogens in cigarette smoke, and smokers with these variants incur a greater risk of lung cancer. Similarly, individuals whose peripheral blood lymphocytes show more numerous chromosomal breakages after exposure to tobacco-related carcinogens (mutagen sensitivity genotype) have a greater than 10-fold higher risk of developing lung cancer as compared with controls, presumably because of genetic variation in genes involved in DNA repair.

The histologic changes that correlate with steps along the path to neoplastic transformation are best documented for squamous cell carcinoma and are described in more detail later. There is a linear correlation between the intensity of exposure to cigarette smoke and the appearance of ever more worrisome epithelial changes. These begin with rather innocuous-appearing basal cell hyperplasia and squamous metaplasia and progress to squamous dysplasia and carcinoma in situ, the last stage before progression to invasive cancer.

Industrial Hazards. Certain industrial exposures, such as asbestos, arsenic, chromium, uranium, nickel, vinyl chloride, and mustard gas, increase the risk of developing lung cancer. High-dose ionizing radiation is carcinogenic. There was an increased incidence of lung cancer among survivors of the Hiroshima and Nagasaki atomic bomb blasts, as well as in workers heavily involved in clean-up after the Chernobyl disaster. Uranium is weakly radioactive, but lung cancer rates among nonsmoking uranium miners are four times higher than those in the general population, and among smoking miners they are about 10 times higher. Asbestos exposure also increases the risk for lung cancer development. The latent period before the development of lung cancer is 10 to 30 years. Lung cancer is the most frequent malignancy in individuals exposed to asbestos, particularly when coupled with smoking. Asbestos workers who do not smoke have a five-fold greater risk of developing lung cancer than do nonsmoking control subjects, whereas those who smoke have a 55-fold greater risk.

Air Pollution. It is uncertain whether air pollution, by itself, increases the risk of lung cancer, but it likely adds to the risk in those who smoke or are exposed to secondhand smoke. It may do so through several different mechanisms. Chronic exposure to air particulates in smog may cause lung irritation, inflammation, and repair, and you will recall that chronic inflammation and repair increases the risk of a variety of cancers (Chapter 7). A specific form of air pollution that may contribute to an increased risk of lung cancer is radon gas. Radon is a ubiquitous radioactive gas that has been linked epidemiologically to increased lung cancer in uranium miners. Other underground miners and workers in locations below ground, such as subways, tunnels, and basements, are at increased risk for radon exposure. This has generated concern that low-level exposure (e.g., in well-insulated homes in areas with naturally high levels of radon in soil) may also increase the incidence of lung cancer.

Acquired Mutations. As with other cancers (Chapter 7), smoking-related carcinomas of the lung arise by a stepwise accumulation of oncogenic "driver" mutations that result in the neoplastic transformation of pulmonary epithelial cells. Some of the genetic changes associated with cancers can be found in the "benign" bronchial epithelium of smokers without lung cancers, suggesting that large areas of the respiratory mucosa are mutagenized by exposure to carcinogens in tobacco smoke ("field effect"). On this fertile soil, cells that accumulate just the "wrong" panoply of complementary driver mutations to acquire all of the hallmarks of cancer develop into carcinomas.

The major histologic subtypes of lung cancer each have distinctive molecular features, as follows:

- *Adenocarcinoma* is associated with tobacco smoking, but less so than other histologic subtypes; as a result, it is the most common subtype in never-smokers (described below). About one-third of adenocarcinomas have oncogenic gain-of-function mutations involving components of growth factor receptor signaling pathways; these are important to recognize because they often can be targeted with specific inhibitors (discussed later). These include gain-of-function mutations in genes encoding several different receptor tyrosine kinases, such as: *EGFR,* in 10% to 15% of tumors in Caucasians and a higher percentage of nonsmoking Asian women; *ALK,* in 3% to 5% of tumors;

ROS1, in 1% of tumors; *MET*, in 2% to 5% of tumors; and *RET*, in 1% to 2% of tumors. Other tumors have gain-of-function mutations in serine/threonine kinases (*BRAF*, 2% of tumors, and *PI3K*, 2% of tumors) or in the *KRAS* gene (roughly 30% of tumors), all of which encode signaling molecules that lie downstream of receptor tyrosine kinases in growth factor signaling pathways.

- *Squamous cell carcinoma* is highly associated with exposure to tobacco smoke and harbors diverse genetic aberrations, many of which are chromosome deletions involving tumor suppressor loci. These losses, especially those involving 3p, 9p (site of the *CDKN2A* gene), and 17p (site of the *TP53* gene), are early events in tumor evolution, being detected at an appreciable frequency in the histologically normal respiratory mucosal cells of smokers. Most tumors have mutations in *TP53*, and p53 protein overexpression (as seen by immunohistochemical staining), a marker of *TP53* mutations, is an early event, being reported in 10% to 50% of squamous dysplasias and 60% to 90% of squamous cell carcinoma in situ. The *CDKN2A* tumor suppressor gene, which encodes the cyclin-dependent kinase inhibitor p16, is mutated in 65% of tumors. Many squamous cell carcinomas also have amplification of *FGFR1*, a gene encoding the fibroblast growth factor receptor tyrosine kinase.
- *Small cell carcinoma* is virtually always smoking related and has the highest mutational burden among lung cancers. There is almost universal inactivation of both *TP53* and *RB*, and unusual transformations of non–small cell carcinoma to small cell carcinoma are often associated with acquisition of *RB* loss-of-function mutations, emphasizing the importance of *RB* inactivation in this lung cancer subtype. Loss of chromosome 3p also occurs in nearly all of these tumors and is seen even in histologically normal lung epithelium, suggesting that this also is a critical early event. This subtype is also commonly associated with amplification of genes of the *MYC* family.

Lung Cancer in Never-Smokers. The WHO estimates that 25% of lung cancer worldwide occurs in never-smokers. This percentage is probably closer to 10% to 15% in Western countries. These cancers occur more commonly in women, and most are adenocarcinomas, often with targetable mutations/co-mutations. Cancers in nonsmokers are more likely to have *EGFR* mutations and almost never have *KRAS* mutations; *TP53* mutations are not uncommon, but occur less frequently than in smoking-related cancers.

Precursor (Preinvasive) Lesions. Four types of morphologic precursor epithelial lesions are recognized: (1) atypical adenomatous hyperplasia, (2) adenocarcinoma in situ, (3) squamous dysplasia and carcinoma in situ, and (4) diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. It should be remembered that the term *precursor* does not imply that progression to cancer is inevitable. Currently it is not possible to distinguish between precursor lesions that progress and those that remain localized or regress.

Classification

Tumor classification is important for consistency in patient treatment and provides a uniform basis for epidemiologic and biologic studies. The most recent classification of lung cancer is given in Table 15.9. Several histologic variants of each type of lung cancer are described; however, their clinical significance is still undetermined except as mentioned herein. The relative proportions of the major categories are:

- Adenocarcinoma (50%)
- Squamous cell carcinoma (20%)
- Small cell carcinoma (15%)
- Large cell carcinoma (2%)
- Other (13%)

There may be mixtures of histologic patterns, even in the same cancer. Thus combinations of squamous cell carcinoma and adenocarcinoma or small cell and squamous cell carcinoma occur in about 14% and 5% of patients, respectively.

The incidence of adenocarcinoma has increased significantly in the last 2 decades, and it is now the most common form of lung cancer in women and men. The basis for this change is unclear. One possible factor is the increase in women smokers, but this only highlights our ignorance about why women develop adenocarcinoma more frequently. Another possibility is that changes in cigarettes (altered filter tips and decreased tar and nicotine) may have caused smokers to inhale more deeply, increasing the exposure of peripheral airways and cells with a predilection to give rise to adenocarcinoma to carcinogens.

Table 15.9 Histologic Classification of Malignant Epithelial Lung Tumors

Tumor Classification
Adenocarcinoma
Lepidic, acinar, micropapillary, papillary, solid (according to predominant pattern)
Invasive mucinous adenocarcinoma
Minimally invasive adenocarcinoma (nonmucinous, mucinous)
Squamous cell carcinoma
Keratinizing, nonkeratinizing, basaloid
Neuroendocrine tumors
Small cell carcinoma
Combined small cell carcinoma
Large cell neuroendocrine carcinoma
Combined large-cell neuroendocrine carcinoma
Carcinoid tumor
Typical, atypical
Other uncommon types
Large cell carcinoma
Adenosquamous carcinoma
Sarcomatoid carcinoma
Pleomorphic, spindle cell, giant cell carcinoma, carcinosarcoma, pulmonary blastoma
Others such as lymphoepithelioma-like carcinoma and NUT carcinoma
Salivary gland–type tumors

MORPHOLOGY

Lung carcinomas may arise in the peripheral lung (more often adenocarcinomas) or in the central/hilar region (more often squamous cell carcinomas), sometimes in association with recognizable precursor lesions.

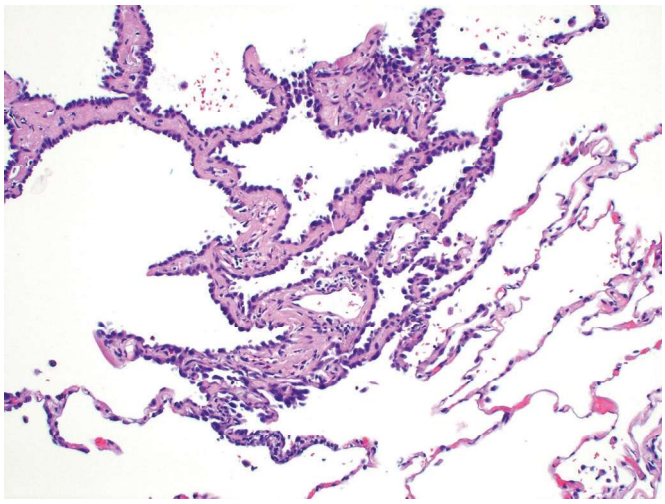

Figure 15.41 Atypical adenomatous hyperplasia. The epithelium is cuboidal, and there is mild interstitial fibrosis.

Atypical adenomatous hyperplasia is a small precursor lesion (≤5 mm) characterized by dysplastic pneumocytes lining alveolar walls that are mildly fibrotic (Fig. 15.41). It can be single or multiple and can be in the lung adjacent to invasive tumor or away from it.

Adenocarcinoma in situ (formerly called bronchioloalveolar carcinoma) is a lesion that is less than 3 cm in size and is composed entirely of dysplastic cells growing along pre-existing alveolar septa. The cells have more dysplasia than atypical adenomatous hyperplasia and may or may not have intracellular mucin (Fig. 15.42).

Adenocarcinoma is an invasive malignant epithelial tumor with glandular differentiation or mucin production by the tumor cells. Adenocarcinomas grow in various patterns, including acinar, lepidic, papillary, micropapillary, and solid. Compared with squamous cell cancers, these lesions are usually more peripherally located and tend to be smaller. They vary histologically from well-differentiated tumors with obvious glandular elements (Fig. 15.43A), to papillary lesions resembling other papillary carcinomas, to solid masses with only occasional mucin-producing glands and cells. The majority express thyroid transcription factor-1 (TTF-1) (Fig. 15.43A inset), a protein first identified in the thyroid that is required for normal lung development. At the periphery of the tumor there is often a lepidic pattern of spread, in which the tumor cells "crawl" along normal-appearing alveolar septa. Tumors (≤3 cm) with a small invasive component (≤5 mm) associated with scarring and a peripheral lepidic growth pattern are called **microinvasive adenocarcinoma.** These have a far better prognosis than invasive carcinomas of the same size. **Mucinous adenocarcinomas** tend to spread aerogenously, forming satellite tumors; thus, these are less likely to be cured by surgery. They may present as a solitary nodule or as multiple nodules, or an entire lobe may be consolidated by tumor, mimicking lobar pneumonia.

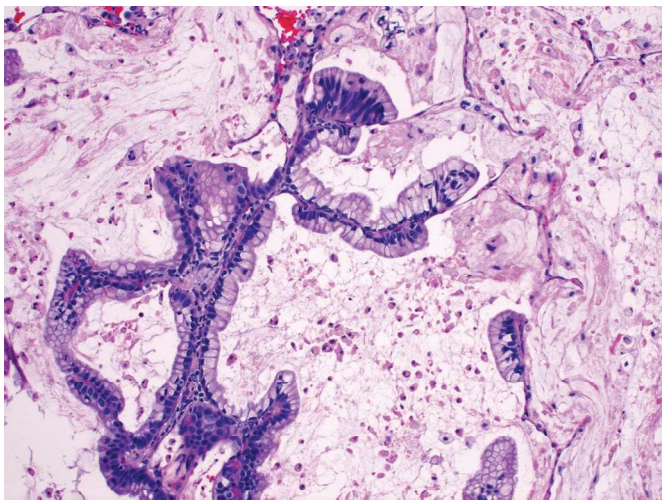

Figure 15.42 Adenocarcinoma in situ, mucinous subtype. Characteristic growth along pre-existing alveolar septa is evident, without invasion.

Squamous cell carcinoma is more common in men and is strongly associated with smoking. Precursor lesions that give rise to invasive squamous cell carcinoma are well characterized. Squamous cell carcinomas are often antedated by **squamous metaplasia** or **dysplasia** in the bronchial epithelium, which then transforms to **carcinoma in situ,** a phase that may last for years (Fig. 15.44). By this time, atypical cells may be identified in cytologic smears of sputum or in bronchial lavage fluids or brushings (Fig. 15.45), but the lesion is asymptomatic and undetectable on radiographs. Eventually, an invasive squamous cell carcinoma appears. The tumor may then follow a variety of paths. It may grow exophytically into the bronchial lumen, producing an intraluminal mass. With further enlargement the bronchus becomes obstructed, leading to distal atelectasis and infection. The tumor may also penetrate the wall of the bronchus and infiltrate along the peribronchial tissue (Fig. 15.46) into the adjacent carina or mediastinum. In other instances, the tumor grows along a broad front to produce a cauliflower-like intraparenchymal mass that compresses the surrounding lung. As in almost all types of lung cancer, the neoplastic tissue is gray-white and firm to hard. Especially when the tumors are bulky, focal areas of hemorrhage or necrosis may appear to produce red or yellow-white mottling and softening. Sometimes these necrotic foci cavitate.

Histologically, squamous cell carcinoma is characterized by the presence of keratinization and/or intercellular bridges. Keratinization may take the form of squamous pearls or individual cells with markedly eosinophilic cytoplasm (see Fig. 15.43B). These features are prominent in well-differentiated tumors, are easily seen but not extensive in moderately 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 arose centrally from the segmental or subsegmental bronchi, but 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 (see Fig. 15.44).

Small cell carcinoma is a highly malignant tumor with a strong relationship to cigarette smoking; only about 1% occurs in nonsmokers. Tumors may arise in major bronchi or in the periphery of the lung. There is no known pre-invasive 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

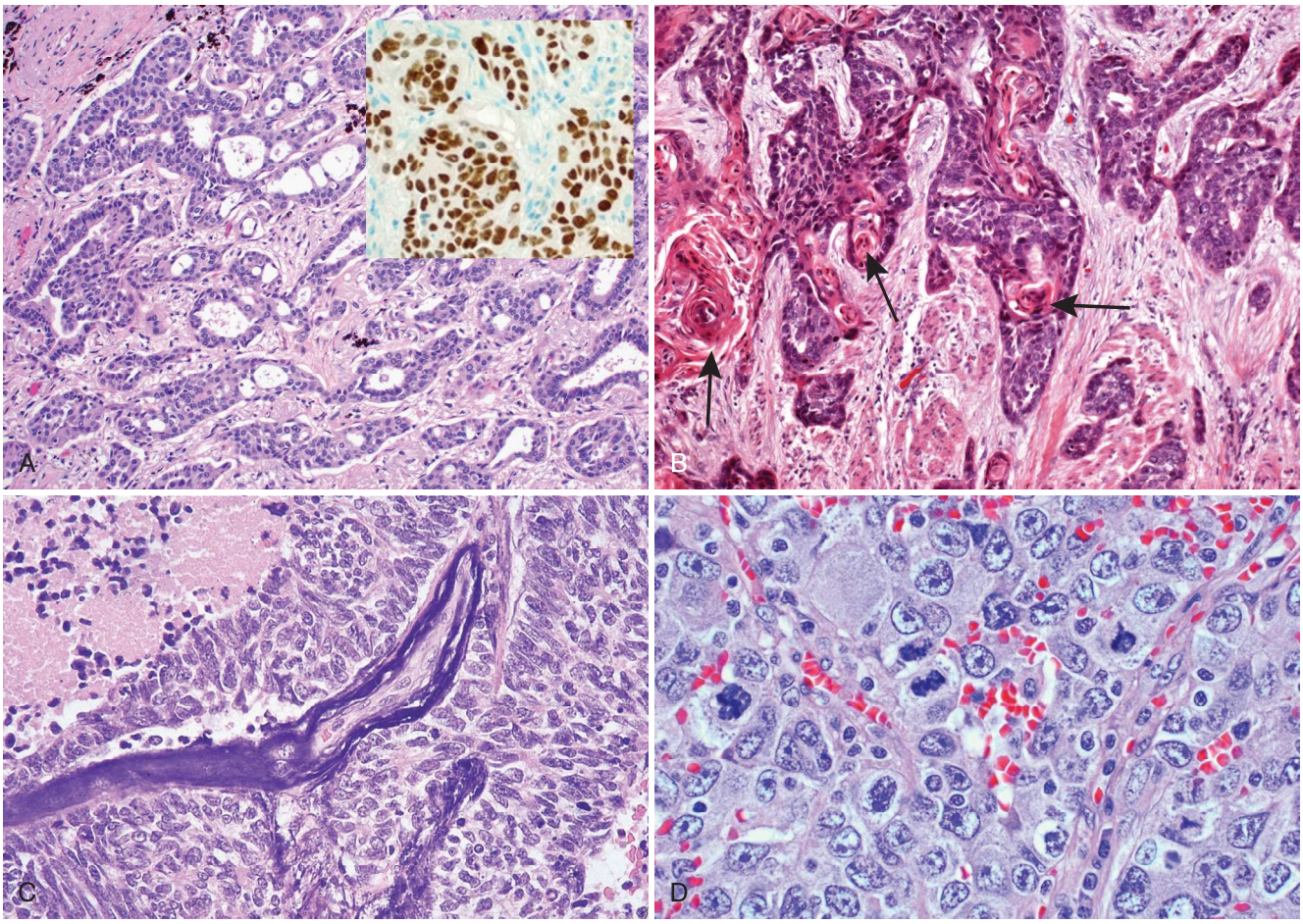

Figure 15.43 Histologic variants of lung carcinoma. (A) Gland-forming adenocarcinoma; *inset* shows thyroid transcription factor 1 (TTF-1) expression, as detected by immunohistochemistry. (B) Well-differentiated squamous cell carcinoma showing keratinization *(arrow)*. (C) Small cell carcinoma. There are islands of small, deeply basophilic cells and areas of necrosis. (D) Large cell carcinoma. The tumor cells are pleomorphic and show no evidence of squamous or glandular differentiation.

chromatin (salt and pepper pattern), and absent or inconspicuous nucleoli (see Fig. 15.43C). 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 times the diameter of a small resting lymphocyte (a size of about 25 μm). 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. 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 or even spindled cell morphologies resembling sarcoma.

Electron microscopy shows dense-core neurosecretory granules, about 100 nm in diameter, in two-thirds of cases of small cell carcinoma. The occurrence of neurosecretory granules; the expression of neuroendocrine markers such as chromogranin, synaptophysin, and CD56; 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. This simplistic idea is challenged, however, by the existence of tumors comprised of a mixture of small cell carcinoma and other histologies and well-documented "transformations" of non–small cell carcinoma to small cell carcinoma. Among the various types of lung cancer, small cell carcinoma is the one that is most commonly associated with ectopic hormone production (discussed later).

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 (see Fig. 15.43D). Large cell carcinoma is a diagnosis of exclusion since it expresses none of the markers associated with adenocarcinoma (TTF-1, napsin A) or squamous cell carcinoma (p40, p63). One histologic variant is large cell neuroendocrine carcinoma, which has molecular features similar to those of small cell carcinoma, but is comprised of tumor cells of larger size.

Combined Carcinoma. Approximately 4% to 5% of all lung carcinomas have a combined histology, including two or more of the aforementioned types.

Any type of lung carcinoma may extend to the pleural surface and then spread within the pleural cavity or into the pericardium. Metastases to the bronchial, tracheal, and mediastinal nodes can

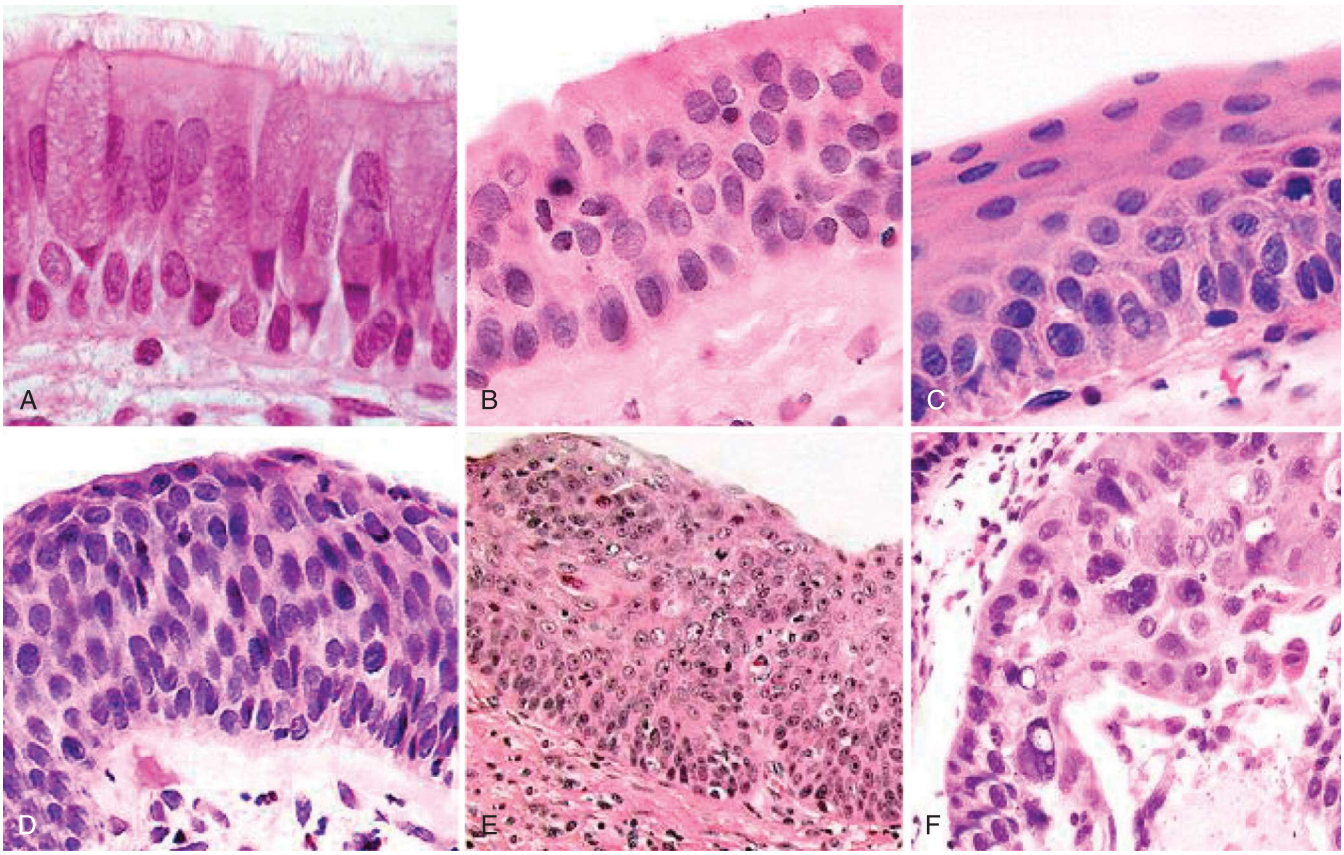

Figure 15.44 Precursor lesions of squamous cell carcinomas. Some of the earliest ("mild") changes in smoking-damaged respiratory epithelium include goblet cell hyperplasia (A), basal cell (or reserve cell) hyperplasia (B), and squamous metaplasia (C). More ominous changes include the appearance of squamous dysplasia (D), characterized by the presence of disordered squamous epithelium, with loss of nuclear polarity, nuclear hyperchromasia, pleomorphism, and mitotic figures. Squamous dysplasia may progress through the stages of mild, moderate, and severe dysplasia. Carcinoma in situ (E), the stage immediately preceding invasive squamous carcinoma (F), by definition has not penetrated the basement membrane and has cytologic features similar to those in frank carcinoma. (A–E, Courtesy Dr. Adi Gazdar, Department of Pathology, University of Texas, Southwestern Medical School, Dallas, Tex. F, Reproduced with permission from Travis WD, et al, editors: *World Health Organization Histological Typing of Lung and Pleural Tumors*, Heidelberg, 1999, Springer.)

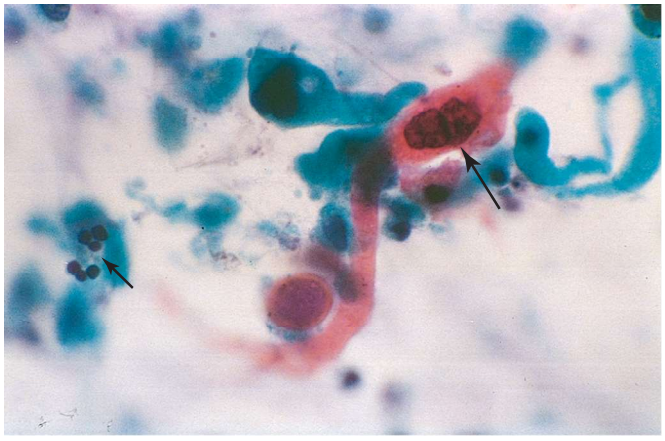

Figure 15.45 Cytologic diagnosis of lung cancer. A sputum specimen shows an orange-staining, keratinized squamous carcinoma cell with a prominent hyperchromatic nucleus *(large arrow)*. Note the size of the tumor cells compared with normal neutrophils *(small arrow)*.

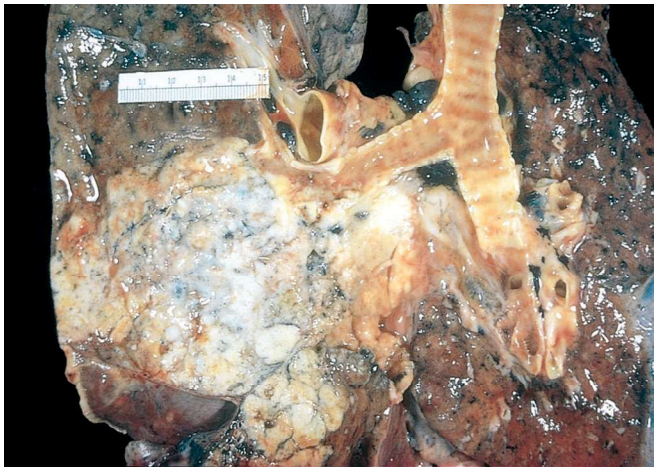

Figure 15.46 Lung carcinoma. The gray-white tumor infiltrates the lung parenchyma. Histologic sections identified this tumor as a squamous cell carcinoma.

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 late outside the thorax. Metastasis may be the first manifestation of an underlying occult pulmonary lesion. No organ or tissue is spared, but the adrenal glands, for obscure reasons, are involved in more than half of the cases. The liver (30% to 50%), brain (20%), and bone (20%) are other favored sites of metastases.

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 congestion and edema of the head and arm and, ultimately, circulatory compromise—the **superior vena cava syndrome.** Extension to the pericardial or pleural sacs may cause **pericarditis** (Chapter 12) or **pleuritis** with significant effusions. 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*.

Staging. A uniform TNM system for staging cancer according to its anatomic extent at the time of diagnosis is useful, particularly for comparing treatment results from different centers (Table 15.10).

Table 15.10 International Staging System for Lung Cancer

TNM Staging			
Tis	Carcinoma in situ Adenocarcinoma in situ: adenocarcinoma with pure lepidic pattern, ≤3 cm Squamous cell carcinoma in situ		
T1	Tumor ≤3 cm without pleural or mainstem bronchus involvement (T1mi, minimally invasive adenocarcinoma; T1a, <1 cm; T1b, 1–2 cm; T1c, 2–3 cm)		
T2	Tumor 3–5 cm or involvement of mainstem bronchus but not of carina, visceral pleural involvement, or lobar atelectasis (T2a, 3–4 cm; T2b, 4–5 cm)		
T3	Tumor >5–7 cm or one with involvement of parietal pleura, chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, or separate tumor nodules in the same lobe		
T4	Tumor >7 cm or any tumor with invasion of mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina, or separate tumor nodules in a different ipsilateral lobe		
N0	No metastasis to regional lymph nodes		
N1	Ipsilateral intraparenchymal or peribronchial or hilar nodal involvement		
N2	Metastasis to ipsilateral mediastinal or subcarinal lymph nodes		
N3	Metastasis to contralateral mediastinal or hilar lymph nodes, ipsilateral or contralateral scalene, or supraclavicular lymph nodes		
M0	No distant metastasis		
M1	Distant metastasis (M1a, separate tumor nodule in contralateral lobe or pleural nodules or malignant pleural or pericardial effusion; M1b, single extrathoracic metastasis in a single organ; M1c, multiple extrathoracic metastases)		
Stage Grouping			
Stage 0	Tis	N0	M0
Stage IA	IA1, T1mi or T1a; IA2, T1b; IA3, T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0 N1	M0 M0
Stage IIB	T2b T1a, T1b, T1c, T2a, T2b T3	N0 N1 N0	M0 M0 M0
Stage IIIA	T1a, T1b, T1c, T2a, T2b T3 T4	N2 N1 N0, N1	M0 M0 M0
Stage IIIB	T1a, T1b, T1c, T2a, T2b T3, T4	N3 N2	M0 M0
Stage IIIC	T3, T4	N3	M0
Stage IVA	T any	N any	M1a, M1b
Stage IVB	T any	N any	M1c

Clinical Features

Lung cancer is one of the most insidious and aggressive neoplasms in the realm of oncology. In the usual case it is discovered in patients in their 50s or older whose symptoms are of several months' duration. The major presenting complaints are cough (75%), weight loss (40%), chest pain (40%), and dyspnea (20%). Some of the more common local manifestations of lung cancer and their pathologic bases are listed in Table 15.11.

Not infrequently, lung cancer is recognized though biopsy of tissues involved by metastatic disease. Symptoms of metastases depend on the site, for example, back pain in bone metastases and headache, hemiparesis, cranial nerve damage, and seizures in brain metastases.

The best "treatment" for lung cancer is smoking prevention, which has lowered lung cancer incidence in the United States among men; however, 15% of adults still smoke, and even those who quit remain at elevated risk for an extended period of time. This reality has led to early detection trials in high-risk individuals using low-dose computed tomography, which is capable of detecting some early (resectable) non–small cell lung cancers, but at a cost of a high incidence of false-positive (noncancer) findings. Overall, the outlook is poor for most patients. Even with incremental improvements in thoracic surgery, radiation therapy, and chemotherapy, the overall 5-year survival rate is only 18.7%. The 5-year survival rate is 52% for cases detected when the disease is still localized, 22% when there is regional metastasis, and only 4% with distant metastases. In general, adenocarcinoma and squamous cell carcinoma tend to remain localized longer and have a slightly better prognosis than small cell carcinoma, which is usually advanced by the time it is discovered.

Table 15.11 Local Effects of Lung Tumor Spread

Clinical Feature	Pathologic Basis
Cough (50%–75%)	Involvement of central airways
Hemoptysis (25%–50%)	Hemorrhage from tumor in airway
Chest pain (20%)	Extension of tumor into mediastinum, pleura, or chest wall
Pneumonia, abscess, lobar collapse	Airway obstruction by tumor
Lipoid pneumonia	Tumor obstruction; accumulation of cellular lipid in foamy macrophages
Pleural effusion	Tumor spread into pleura
Hoarseness	Recurrent laryngeal nerve invasion
Dysphagia	Esophageal invasion
Diaphragm paralysis	Phrenic nerve invasion
Rib destruction	Chest wall invasion
SVC syndrome	SVC compression by tumor
Horner syndrome	Sympathetic ganglia invasion
Pericarditis, tamponade	Pericardial involvement

SVC, Superior vena cava.

Treatment of patients with adenocarcinoma and activating mutations in *EGFR* (present in about 15% of all cases) or in other tyrosine kinases with specific kinase inhibitors prolongs survival. Many tumors that recur carry new mutations that generate resistance to these inhibitors, proving that these drugs are "hitting" their target. In contrast, activating *KRAS* mutations (present in approximately 30% of cases of adenocarcinoma) appear to be associated with a worse prognosis, regardless of treatment, in an already grim disease. Because of the mutagenic effects of carcinogens in tobacco smoke, lung cancers have a high burden of potentially antigenic neoantigens. Accordingly, both adenocarcinoma and squamous cell carcinoma respond in subsets of cases to checkpoint inhibitor therapy, which has produced improvements in survival and is now approved for use.

Small cell carcinoma is quite sensitive to radiation therapy and chemotherapy, and approximately 10% of patients with limited disease survive for 5 years and may be cured. Unfortunately, however, most patients present with advanced stage disease; for these patients, despite excellent initial responses to chemotherapy, the median survival is approximately 10 months and the cure rate is close to zero. New approaches involving use of antibody-drug conjugates that deliver chemotherapy selectively to tumor cells and immune checkpoint inhibitors are being tested.

Paraneoplastic Syndromes. Lung carcinoma can be associated with several paraneoplastic syndromes (Chapter 7), some of which may antedate the development of a detectable pulmonary lesion. The hormones or hormone-like factors elaborated by lung cancer cells and associated syndromes 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 paraneoplastic 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 27), in which muscle weakness is caused by autoantibodies (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.

KEY CONCEPTS

CARCINOMAS OF THE LUNG

- The three major histologic subtypes are adenocarcinoma (most common), squamous 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 *MET* mutations.
- Smoking is the most important risk factor for lung cancer; the most common subtype related to smoking in men and women is adenocarcinoma. Adenocarcinoma also is the most common subtype in non-smokers.
- Precursor lesions include atypical adenomatous hyperplasia and adenocarinoma in situ (formerly bronchioloalveolar carcinoma) for adenocarcinomas and squamous dysplasia for squamous cell carcinoma.
- Tumors 3 cm or less in diameter characterized by pure growth along pre-existing structures (lepidic pattern) without stromal invasion are now called adenocarcinoma in situ.
- Lung cancers, particularly small cell lung carcinomas, often 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. Virtually all pulmonary neuroendocrine cell hyperplasias are secondary to airway fibrosis and/or inflammation. The exception is a rare disorder called *diffuse idiopathic*