Aspiration, Bronchial Obstruction, Bronchiectasis, and Related Disorders

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The conducting airways play a pivotal role in the spectrum of pulmonary pathology, not only as conduits for injurious agents to enter the lung, but also as an anatomic compartment that is affected by a diverse array of primary or secondary bronchocentric diseases. This chapter discusses aspiration and bronchial obstruction in detail, with emphasis on the aspiration of toxic, infective, or particulate matter. Lung abscess, a frequent complication of obstruction or aspiration, is also reviewed. Both aspiration and lung abscess are reconsidered within the context of pulmonary infectious disease mainly in Chapter 8 on bacterial infections, and to some extent in the chapters on mycobacterial (Chapter 9), fungal (Chapter 10), and parasitic diseases (Chapter 14).

Bronchiectasis, which is frequently grouped with other forms of obstructive lung disease (see Chapter 24), is discussed in this chapter as a major pathway of airway remodeling that may be of inflammatory, postobstructive, or congenital etiology, and is, itself, an important sequela of aspiration. The topic of bronchiectasis cannot be considered without reference to inflammatory lesions of the small airways, which may follow or precede the development of bronchiectasis (see Chapter 25). The present chapter also discusses a variety of pulmonary disorders that may simulate, initiate, or complicate bronchiectasis.

Involvement of the large airways in systemic diseases such as amyloidosis (Chapter 21), sarcoidosis (Chapter 18), collagen vascular diseases, including relapsing polychondritis (Chapter 20), connective tissue disorders such as Marfan’s syndrome (Chapter 20), or as a complication of environmental dust exposures (Chapter 26) is reviewed in each of their respective chapters. An excellent review of bronchiectasis in systemic diseases is that by Cohen and Sahn.¹

A discussion of asthma and its related conditions of mucoid impaction, bronchocentric granulomatosis, and allergic bronchopulmonary aspergillosis can be found in Chapter 15. Unique congenital lesions of the airways in addition to the enigmatic intralobar sequestration are discussed respectively in Chapters 6 and 7 on pediatric lung pathology. A variety of degenerative or so-called metabolic disorders that affect the large airways, such as tracheobronchopathia osteoplastica, are reviewed in Chapter 21. Finally, bronchial tumors are extensively covered throughout volume 2, which is devoted to pulmonary neoplasia.

Aspiration

Aspiration is the inhalation of liquid or solid materials into the lower respiratory tract, usually from the oral or nasal cavities, oropharynx, esophagus, or stomach. Logically, the course of aspiration is determined by such laws of physics as inertia and gravity. Larger, more solid materials, and finer more liquid materials, all follow the straightest and most dependent course after they enter the trachea. As explained in Chapter 2, the right mainstem bronchus continues on a more direct course than the left (20 to 30 degrees compared to 40 to 60 degrees for the left mainstem bronchus); the wider angle of the left bronchus allows it to extend around the heart. Larger, more solid objects that pass the larynx often lodge in the right mainstem bronchus, while smaller solid objects most frequently continue into the right lower lobe bronchus.² This has been well demonstrated in the aspiration of foreign objects by children, generally in the age group of 1 to 3 years.³⁴ During this age range, children examine almost everything by placing items into their mouths. In both children and adults, larger objects are sometimes stopped at the larynx and may be expelled by strong coughing. In adults, sudden death due to laryngeal obstruction by aspirated food (most frequently meat) has been termed the café coronary.⁵

More than 80% of aspirated foreign bodies occur in children, and among all age groups only 5% are spontaneously expectorated.⁶⁷ Sharper objects may perforate a
FIGURE 5.1. Foreign-body aspiration. Fragment of chicken bone (arrow) wedged into junction of lobar bronchi has caused acute hemorrhage and was the reason for emergency resection before bronchoscopic diagnosis.

Young children most frequently aspirate peanuts, beads, and other fragments of wooden or plastic toys. Peanuts and sunflower seeds lead the list in Western countries, whereas in Arabic countries children most often aspirate melon seeds. Older children may inhale flowering grass fragments, which wedge themselves into more distal bronchi and resist expectoration. In any age group, teeth, fragments of bone (Fig. 5.1), food, blood clots, tissue fragments, nasal pack components, lipids from oily nose drops or orally administered cathartics, bacterial fragments, and gastric content most commonly enter the lung. Noguchi et al. reported a subacute reaction to mud aspiration in a victim of near-drowning, while aspiration of sand in children has been reported to cause a radiographic “sand bronchogram.”

Aspiration need not only be from external sources. Rupture of large fluid-filled abscess cavities, tuberculous cavities, or other cysts might be followed by intrabronchial aspiration of infective or other types of material into dependent zones (see Fig. 9.7 in Chapter 9).

The most common conditions predisposing to aspiration include impaired consciousness, most frequently bronchus and cause bleeding, or even penetrate the pleural cavity and cause pneumothorax. A foreign body may migrate within the bronchi and cause wandering infiltrates.

Aspiration of sand in children has been reported to cause a radiographic “sand bronchogram.” Drowning, often thought of as occurring in fresh or salt water, has also occurred in large vats of beer, wine, liquid chocolate, and other interesting concoctions. A literary example of this is Shakespeare’s Richard III, in which the Duke of Clarence is finally dispatched in a large vat of wine (the “malmsey butt”).

Brock in 1942, beautifully illustrated the mechanics of aspiration with abscess formation, which most often followed the dependent course described. Once within the lung, finer and more fluid ingredients flow into the first dependent orifices that are encountered. In the supine position, these are most often the posterior segment of the upper lobe and superior segment of the lower lobe (Fig. 5.2). In the more upright position, material flows preferentially into the basilar segments of the lower lobes. The basilar segments divide rather evenly, and localization within these segments is not as discrete as in other areas of the lung. When a person is in the lateral decubitus position, the axillary branches of the subsegments of apical and posterior upper lobe bronchi are favored. The more anterior portions of the lung are usually spared the effects of aspiration, unless aspiration occurs in the prone position, as in near-drowning.

FIGURE 5.2. Routes of aspiration. Corrosion cast and diagram of bronchial tree show left lung to illustrate effects of position on eventual course of aspiration. In addition to zone of aspiration marked, dependent upper-lobe posterior segment is common site of involvement, as would be more obvious on cast of right lung. (From Brock RC. Lung Abscess. Springfield, IL: Charles C. Thomas, 1952:10, with permission.)
from alcohol, drugs, or anesthesia, followed by central nervous system disorders (e.g., epilepsy, stroke, dementia) or neuromuscular diseases. Next in frequency is aspiration secondary to obstructing masses or other functional defects of the esophagus or stomach. Episodes of aspiration are eventually confirmed in about 85% of children, but in only about 30% of adults. The difference in documentation is probably related to the altered level of consciousness in adults causing temporary amnesia. The common clinical manifestations of an aspirated foreign body constitute a triad of cough, wheezing or rhonchi, and decreased air entry. The wheezing that is sometimes associated with aspirated foreign bodies in children may be ameliorated with theophylline, leading to diagnostic confusion with asthma.

Early experimental animal studies showed that aspiration of material into the lungs regularly occurs when materials are placed in the nares or accessory sinuses during anesthesia. Myerson found blood immediately postoperatively in the tracheobronchial tree in 79% to 100% of humans who underwent tonsillectomy, including those under general or local anesthesia. Several experimental studies have also proven that normal adults aspirate with some regularity. Quinn and Meyer in 1929 introduced lipiodal (iodinated poppy seed oil) into the noses of sleeping subjects and found the material often entered the lungs. Amberson in 1937 reported placing barium in the mouths of normal subjects during sleep, with similar results. Radiologists sometimes observe aspiration while performing upper gastrointestinal tract barium studies (see below). As reviewed by Bartlett, various markers placed in the stomach the night prior to surgery have been identified in lungs sampled during surgery the next day in 7% to 16% of patients. Huxley and associates refined these techniques by placing indium-111 chloride in the posterior nasopharynx periodically during sleep. On lung scanning, this tracer was found in the lungs of 45% of normal individuals and in 70% of those with some alteration of the central nervous system. Those in the normal group who did not aspirate were fitful sleepers who tended not to enter deep sleep. The implication is that most normal people who enter deep sleep, aspirate. Nasogastric and oropharyngeal tubes, including endoscopes and tracheostomy tubes, increase the risk of aspiration.

Normal individuals tend to clear such occult aspirations without difficulty or sequelae. An acute cough reflex is most important, but also valuable are intact mucociliary activity and alveolar macrophage response (see Chapter 3). The pathologic effects of aspiration are dependent on the character, volume, and frequency of the aspirated components. In this chapter, food and medicinals, gastric acid, lighter hydrocarbons, and heavier oils are separately considered. Aspirated bacteria are covered in the section on abscess formation. Retained squamous cells from meconium in newborns are a sign of in utero distress. Squamous cells in the lungs of adults are an indicator of oral, oropharyngeal, or esophageal aspiration (Fig. 5.3). In the absence of other evidence of aspiration, finding mixed bacteria in lung tissue is very suggestive of aspiration of oral content.

Gastric Acid

Lung injury following aspiration has been subdivided by Marik into aspiration pneumonitis and aspiration pneumonia. Aspiration pneumonitis refers to acute chemical lung injury due to inhaled gastric acid with or without injury due to aspirated particulate matter, whereas aspiration pneumonia is an infectious process resulting from the inhalation of oropharyngeal secretions colonized by pathogenic bacteria.

Aspiration of gastric acid, a major cause of acute respiratory distress syndrome (ARDS), has been well studied in humans and in experimental animals. In experimental models, it has been suggested that a pH of 2.4 or lower and a significant quantity of acid (estimated to be 20 to 25 mL in an adult human or 1 to 4 mL/kg in an experimental animal) are necessary to induce a chemical pneumonitis. When gastric acid with methylene blue was put into anesthetized dog tracheas, dye was visible on the pleural surface 12 to 18 seconds later. Atelectasis of lung tissue was noted in 3 minutes. Human studies date from the classic study of Mendelson in 1946, and acute gastric acid aspiration is sometimes called the Mendelson syndrome. Mendelson studied 61 cases of massive gastric aspiration in obstetric patients (0.15% incidence) under ether anesthesia. Respiratory distress occurred soon after aspiration, with accompanying cyanosis, tachypnea, and
tachycardia. Bronchospasm occurred in most of his patients. Chest radiographs initially showed rather widespread mottled densities, most of which cleared by 7 to 10 days. Only eight of 61 patients became infected. This study was conducted before antibiotics were readily available, but other studies in humans with or without antibiotics or steroids have confirmed his findings. In general, later studies have found a lower incidence (about 30%) of bronchospasm, more frequent early temperature elevation, and increased mortality (in the range of 30% to 60%) despite therapy. Hypotension and hypoxemia occurred more commonly than in Mendelson’s series.22 The combination of acid and particulate aspiration exacerbates alveolar capillary injury.30

Bynum and Pierce31 studied 50 patients with well-documented gastric acid aspiration. In their series, all these events followed altered consciousness, most often by a sedative drug overdose or a general anesthesia. As in Mendelson’s experience, respiratory symptoms developed rapidly and were very similar in all patients despite eventual outcome. Three clinical outcomes were described: 12% died shortly after aspiration; 62% had rapid clinical and radiographic clearing on the average of 4.5 days; and 26% had rapid improvement followed by deterioration relating to bacterial infection. Of this latter group 60% died, whereas 28% of the whole group died; death occurred between day 1 and 16, averaging 7.2 days. These authors found initial steroid or antibiotic therapy did not affect eventual outcome.

In both humans and animals, edema, congestion, hemorrhage, and degeneration of bronchiolar lining cells and alveolar type I and II cells follows early in the course (Fig. 5.4). After 4 hours alveoli are filled with polymorphonuclear neutrophils (PMNs) and fibrin. Hyaline membranes are formed by 48 hours, providing a histologic picture of diffuse alveolar damage (DAD) (see Chapter 4). Resolution begins at about 72 hours and may either lead to complete restoration of alveoli or leave some residual scarring. Of course repeated aspiration may lead to combined acute, subacute, and chronic appearances. In his review, Bartlett22 referred to this rapid and irreversible type of injury as comparable to a “flash burn,” and noted that little can be done to prevent injury once acid has made contact with the lung (Fig. 5.4). The reactions just described plus fluid extravasation help to dilute the acid, as do buffering components from serum and cell breakdown products, but these only occur after injury.

More recent studies have indicated that the mechanism of lung injury following acid aspiration extends beyond the direct chemical effects of acid to involve various inflammatory mediators including tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), adhesion molecules, and cyclooxygenase and lipoxygenase products.32-35 The role of reactive oxygen species, and the adverse effect of oxygen administration after an episode of aspiration were demonstrated experimentally by Nader-Djalal et al.36 A primary role is currently placed on neutrophils and complement in mediating lung injury in this setting.27,32,37,38 Thus, aspiration pneumonitis represents a biphasic response composed of early-onset direct pulmonary injury due to acid, followed by delayed injury due to acute inflammation.26,38

Low-grade chronic aspiration of gastric content may escape easy detection. These occult aspirations may lead to interstitial fibrosis, and perhaps account for the 20% to 54% incidence of associated and unexplained pulmonary fibrosis in patients with esophageal abnormalities, most commonly hiatal hernia or simple reflux.30,40 The role of reflux in asthma, chronic bronchitis, chronic cough, recurrent pneumonia, cystic fibrosis, and sudden infant death syndrome has been reviewed by Allen et al. [see also section on cholesterol (endogenous lipid) pneumonia in this chapter].41

**Lighter Hydrocarbons**

Children, particularly those aged 1 to 5 years, are likely to ingest various lighter hydrocarbons, mostly lighter volatile petroleum distillates. These products include kerosene, turpentine, and other paint thinners; furniture or shoe polish; lighter fluid; gasoline; dry cleaning fluids; and some insecticides. The toxicity is greater with those products that disperse most easily, specifically those that cause the greatest decrease in surface tension, or have the least viscosity or the highest volatility.42

Although ingestion precedes aspiration, Eade and associates43 nicely reviewed the reasons that aspiration is the most important toxic pathway of injury. Symptoms develop rapidly and radiographs often show localized pulmonary infiltrates, often in the aspiration zones mentioned earlier. Experimentally, the lethal dose by
FIGURE 5.5. Lentil bean. A. At top is thick outer coat; below, cotyledon compartments with starch cells. B. Cellulose framework of legume cotyledon compartments is birefringent under polarized light. C. Degenerated aspirated vegetable material retains compartmental structure and stains strongly with Gomori methenamine silver.

Food and Medicinals

Various food particles, such as skeletal muscle, fat tissue, or fragments of bone, may be aspirated and identified histologically in lung tissue. Cooking or digestion may result in poorly defined particles that appear foreign but defy further definition. As was well demonstrated by Knoblich and others, portions of legume seeds are one of the better markers of food aspiration. The legumes most commonly eaten are various peas, beans, and peanuts; because they are relatively inexpensive and nutritious, they occur in many products. (The word lentil is sometimes used in these references, but it is also the name of a specific type of bean). The legume seed (Fig. 5.5) consists of a thick cellulose outer coat, the cellulose walls of the inner food storage compartments, and the starch cells contained within these food compartments. Cooking softens the outer shell and cell walls of the beans or peas and allows easy disruption of the content, with a resultant jelling effect of the starch particles (called “thickening” in cooking). The cellulose walls of the outer coat and starch compartments are more difficult to totally disrupt or digest, and therefore act as both a chronic irritant and a good marker of aspiration.

Aspiration of these fragments in both experimental animals and humans produces an acute exudative response within 24 hours (Fig. 5.6), followed by a foreign-body giant cell reaction (Fig. 5.7). These cell wall fragments are Gomori methenamine silver (GMS) positive, and usually birefringent under polarized light (Fig. 5.5). The glycogen compartments, when intact, are vividly periodic acid-Schiff (PAS) positive (Fig. 5.7A). Starch cells may be mistaken histologically for parasite larvae (Fig. 5.6B). At about 10 days (experimentally) an organized granulomatous reaction occurs around the aspirated particles, and eventually the starch cells disappear, leaving only the cellulose fragments.

The walls of carrots, onions, and most nonlegumes digest more readily and do not give rise to as much exuberant chronic reactions as seen with legumes. They do, however, undergo the same type of early changes if aspirated, and initiate acute and subacute pneumonia during digestion of the starch cells. Some of the most offensive aspirated food fragments have undergone alterations in preparation, and some of the worst combinations are
cooking oils and salts, as, for example, an aspirated potato chip (Fig. 5.7B).

Eventually these areas become small fibrotic or fibrocalcific nodules, which may appear almost as degenerated parasites or as sclerosed blood vessels (Fig. 5.8). They may appear as small hyalinized granulomas or possibly as entrapped calcospherites, usually within a fibrous stroma. At times the conditions for aspiration are chronic, and recurrent aspiration leads to the acute and chronic changes together or in close proximity in the same specimen.

Respiratory bronchioles exhibit marked remodeling associated with proliferative bronchiolitis obliterans, foreign-body granulomas, and entrapped food particles. The macroscopic appearance is that of scattered yellow miliary nodules that are reminiscent of miliary...
FIGURE 5.9. Small pale yellow to light brown nodules represent aspiration bronchiolitis obliterans in a debilitated patient with chronic aspiration. Diffuse light brown areas represent generalized organizing pneumonia.

tuberculosis or diffuse panbronchiolitis (Fig. 5.9). Matsuse and colleagues have designated this condition as diffuse aspiration bronchiolitis, which they observed in 31 of 4880 consecutive autopsies (0.64%). The mean age of patients with this condition was 81.2 years. Affected individuals frequently were bed-ridden or had dysphagia due to underlying neurologic disorders. High-resolution computed tomography (HRCT) may show a striking pattern of centrilobular miliary opacities.54

In chronically ill or hospitalized patients, aspirated medicinal products, such as intact or partially digested pharmaceutical tablets, may be associated with aspiration pneumonitis. Inert tablet components such as microcrystalline cellulose, talc, and crospovidone may be identified histologically in conjunction with aspirated food, pneumonia, and foreign-body reaction (see Chapter 26)

FIGURE 5.10. Aspirated tablet filler materials: cellulose (arrow) and crospovidone associated with edema and macrophage response. (From Tomashefski and Felo, with permission from Elsevier.)

Aspirated sodium (or calcium) polystyrene sulfonate (Kayexalate), a potassium-binding cation exchange resin, has a distinctive histologic appearance characterized by large dark eosinophilic or basophilic, angulated, “glassy” particles, that sometimes appear striated (Fig. 5.11).

FIGURE 5.11. Aspirated Kayexalate. A. Chronic inflammatory and foreign-body reaction (arrow) surrounds basophilic Kayexalate particles, obliterating respiratory bronchiole and alveolar duct. B. Angular, “glassy” Kayexalate particles have elicited a foreign-body giant cell reaction.
Kayexalate particles are weakly birefringent, and positive with PAS, acid-fast, and Gram stains, but negative with von Kossa stain.\(^6^0\) Kayexalate has also been identified in tissue sections by infrared microspectrophotometry.\(^6^1\) In humans and experimental animals, Kayexalate has been shown to produce a necrotizing or organizing pneumonia.\(^6^1,6^2\) More frequently, Kayexalate is a cause of mucosal ulcers of the gastrointestinal tract.\(^6^0,6^3\) Kayexalate histologically closely resembles the less frequently encountered material cholestyramine.\(^6^0\) Cholestyramine, however, is more opaque and pink rather than red on acid-fast staining.\(^6^0\)

The aspiration of an intact ferrous sulfate tablet may induce severe, potentially fatal, bronchial mucosal ulceration and hemoptysis.\(^6^4^6^6\) The endoscopic appearance of the ulcerated bronchus typically is of a golden-brown discoloration (Fig. 5.12A).\(^6^4,6^5\) Histologically, ulceration, necrosis, foreign-body reaction, and brown or yellow pigment that stains blue with Prussian blue stain may be seen (Fig. 5.12B). The pathogenesis of this syndrome, colorfully termed “iron lung,” is thought to be a chemical burn induced by oxidation of iron from the ferrous to the ferric form.\(^6^4\)

The radiographic contrast material barium sulfate (\(\text{BaSO}_4\)) is also readily visualized by chest x-ray in patients who aspirate this material. Barium is a fairly inert white powder that tends to produce minimal functional lung impairment. Grossly, following barium aspiration, lung parenchyma is chalky, tan-gray, and slightly indurated (Fig. 5.13A). Histologically, fine, golden-tan, refractile, weakly birefringent particles of barium sulfate are present within the cytoplasm of alveolar macrophages. With chronicity, or upon repeated aspiration, barium-laden macrophages migrate into the interstitium (Fig. 5.13B). Inhalation of barium in the industrial setting (barytosis) is discussed in Chapter 26.

Activated charcoal is sometimes given therapeutically for oral drug overdose. However, if the airway is not protected, charcoal may be aspirated in copious amounts, causing “charcoal lung,” in which coarse black carbon particles obstruct small airways.\(^5^5,6^7\) With prolonged survival following aspiration, bronchiolitis obliterans may develop.\(^6^7\)

![Figure 5.12. A, B. Aspirated ferrous sulfate tablet. A. Bronchoscopic appearance of ulcerated, narrowed airway having a yellow-brown, irregular mucosal surface. B. Bronchial biopsy specimen showing chronic inflammation, fibrosis, and coarse hemosiderin particles. Inset. Prussian blue stain is positive for iron. (Courtesy of Drs. Carol Farver and Atul Mehta, Cleveland Clinic Foundation. From Lee et al.,\(^6^6\) with permission.)](image-url)
Oil Aspiration (Exogenous Lipid) Pneumonia

Oils that may be aspirated include mineral oils such as used in nose drops and cathartics, vegetable oils used in cooking, and animal oils such as cod liver oil or fat-soluble vitamin preparations. Mineral oil, derived from petroleum products, is the most common agent of exogenous lipid pneumonia. Oil aspiration was first described by Laughlen in 1925 in a child who received oily oral and pharyngeal preparations for diphtheria; it was confirmed by him experimentally. The role of oil-based contrast media used for bronchoscopy was well reviewed by Spencer. Animal oils cause a more severe inflammatory reaction than mineral or vegetable oils, and this difference appears related to the number of free fatty acids and increased viscosity of animal oil. Mineral oils are fairly inert, as they have no fatty acids, and are rapidly emulsified and consumed by pulmonary macrophages. Vegetable oil droplets may remain in alveoli for months without eliciting significant reaction, but eventually, due to low-grade chronic irritation, they cause scarring. Animal and mineral oils, but only rarely vegetable oils, may be seen in regional lymph nodes.

Aspiration of oils commonly occurs in older individuals, who may take oily nose drops or cathartics at bedtime. Aspiration most frequently gravitates to the basilar segments of the lower lobes suggesting these patients usually sleep in a more upright position or experience aspiration before reclining. Because of its weakly irritative nature, mineral oil can enter the tracheobronchial tree without stimulating glottic closure or cough reflex. Only two of 14 cases documenting exogenous lipid pneumonia at autopsy had reported significant clinical symptoms during life. Because these oils float in the stomach, it is possible they also are aspirated via reflux from the stomach. In unselected autopsy series, oil aspiration has been documented in 2.5% to 14.6% of adults.

Other oily products that have been incriminated as being aspirated in the lung include fragments of lip balm, burning fats (an occupational exposure), a rapid drying agent in spray enamel paint, oils applied to tobacco products (blackfat tobacco), and possibly hair spray. Children may aspirate oily medications if they are force-fed these while resisting and crying violently. Atypical mycobacteria, particularly rapid growers such as Mycobacterium fortuitum or M. chelonae, have been reported associated with oil aspiration pneumonia (see Chapter 9).

Symptoms of lipid aspiration include fever (39% of patients), weight loss (34%), cough (64%), and dyspnea (50%), although in one large study lipid pneumonia was an incidental finding, without associated symptoms, in 41% of patients. Lung function tests may indicate either obstructive or restrictive changes. Computed tomography (CT) scans usually show alveolar consolidation or ground-glass opacities in the lower lobes. Subfissural clear zones
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FIGURE 5.14. Mineral oil aspiration. A. Surgically excised lung tissue showing glistening, yellow parenchymal consolidation. B. Bronchoalveolar lavage (BAL) fluid from patient who chronically ingested mineral oil as a laxative. Note yellow oil layered on the surface of fluid.

may be interposed between densities, creating a “sandwich effect” on CT scan.68

Grossly, lungs affected by oil aspiration are often gray to yellow and rather solid (Fig. 5.14A). Dense localized fibrotic lesions (paraffinomas) may grossly mimic cancer or complicated pneumoconiosis.68,69 Occasionally oily droplets exude from the cut surface. Microscopically the lipid droplets are often dissolved by tissue processing.71 One exception is cod liver oil, which remains as salmon-colored droplets on hematoxylin and eosin stain after tissue processing. Fats may be seen with rapid water-soluble or oil red O stains on frozen section (Fig. 5.15D); variably sized fat droplets and varying numbers of multinucleate giant cells are present (Fig. 5.15A–C). When only a small amount of fat has been aspirated, the reaction may be contained in alveolar macrophages. This is most commonly seen in mild degrees of aspiration with a diluted fatty substance, as might be seen with milk aspiration. When larger doses of thicker and more toxic oils are aspirated or when oil aspiration is repeated, the areas become densely fibrotic with reduction of the background lung architecture (Fig. 5.14A).89 Occasionally, cor pulmonale results.90,91 Transbronchial biopsies may provide enough tissue to make this diagnosis. Precise identification of specific lipids can be determined by infrared spectrophotometry.88

In the differential diagnosis is artifactual collapse of lung around remnant air bubbles (see Fig. 1.2C in Chapter 1). Exogenous lipid pneumonia can usually be distinguished histologically from endogenous lipid (cholesterol) pneumonia by subdivisions within fat droplets, coarse cytoplasmic vacuoles in macrophages, multinucleated foreign-body giant cell response, and, in more chronic cases, a greater degree of chronic inflammation and fibrosis with destruction of background lung parenchyma in exogenous lipid pneumonia (Fig. 5.15). At times some lipid is incorporated/entrapped in the interstitium (Fig. 5.15C), resembling a similar appearance in diffuse panbronchiolitis and xanthomatous bronchiolitis obliterans (see below and Chapter 25). Diffuse panbronchiolitis is centered more on terminal-respiratory bronchioles and is composed mostly of finely vacuolated fat.

Sputum cytology or cytologic aspiration specimens have been used to confirm lipid pneumonia. On bronchoalveolar lavage an oily layer is sometimes present on the surface of the collection tube (Fig. 5.14B). In 1950, Losner et al.92 using oil stains, found lipid-rich macrophages in 19 of 20 suspected cases in contrast to two of 45 control patients. More recently, Corwin and Irwin93 restudied this situation using bronchoalveolar lavage in various lung diseases including aspiration, hemoptysis, cancer in the lung (either primary or secondary), bronchiectasis, interstitial fibrosis, and sarcoidosis. When compared to normal lungs, samples from diseased lungs in general contained increased fat-filled macrophages. These authors warned that the simple presence of fatty macrophages in cytology preparations is not diagnostic of lipid pneumonia; however, the quantity of lipid was more abundant in aspirators than in these other groups. Their
“aspirator” group consisted mainly of patients with a history of upper gastrointestinal tract disease, including reflux in most. In young children the presence of numerous (>50) oil red O–positive lipid-laden macrophages on tracheal aspirate is highly specific for aspiration. Corwin and Irwin emphasized that the size of the fat droplets in lavage fluid cannot be used to distinguish endogenous from exogenous lipid pneumonia.

**Lung Abscess**

Wherever it occurs, an abscess is a localized accumulation of inflammatory cells, initially having abundant neutrophils, that is usually accompanied by tissue destruction. In the lungs, “cross-country” necrosis occurs during the formation of an abscess (Figs. 5.16 and 5.17). This type of necrosis involves destruction of lung parenchyma, bronchi, and arteries. In contrast, cavities that are more chronic and more slowly formed, such as tuberculous cavities, often leave remnants of fibrotic bronchopulmonary rays coursing through the cavity itself (see Chapter 9). Some more slowly forming nontuberculous abscesses can do this, but most of the abscesses in the lung have an acute initial phase that destroys most of the tissue in the area (Fig. 5.17B). Bronchi frequently connect with abscess cavities, allowing drainage of the necrotic material, leaving an empty or partially empty cavity with or without an air/fluid level on chest radiograph (Figs. 5.18 and 5.19). Occasionally, inflammation seals off all such bronchial connections, resulting in a solid mass that may be suspected of being a tumor. Adjacent organization in acute and subacute abscesses often accounts for an enlarged surrounding radiographic density (Figs. 5.17 and 5.18).

There are many etiologies for cavity formation in the lung, and abscess formation is but one of them. Other
causes include cavitary tumor, cavitary fungal and mycobacterial infections, necrotizing pneumonia, and cystic spaces of assorted etiologies. In 1922, Lockwood reviewed the early history of lung abscesses dating from Hippocrates. Many of the conditions and factors in pulmonary abscess formation, which were already well known by 1922, were summarized in this review. By 1936, a total of 2114 cases had been published.

Aspiration is the most common cause of lung abscess. Other instigators of this type of damage include

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**Figure 5.16.** Abscess cavity formation. “Cross-country” necrosis often occurs in abscess formation. Multiple bronchi often open into such a cavity. (Courtesy of A.A. Liebow Pulmonary Pathology collection, San Diego, California.)

**Figure 5.17.** Acute abscess cavity. **A.** Chest radiograph shows cavity with loss of parenchymal detail internally from drainage of necrotic debris. Note variable thickness of reaction in surrounding lung. Radiodense line is radiographic marker on tube. **B.** Gross specimen. Note cavity is mostly drained, with fresh-appearing, thin lining without fibrous wall. Note also persistence of some trabeculae, presumed bronchopulmonary rays, and variable but narrow surrounding inflammatory reaction.
FIGURE 5.18. Multiple chronic abscess cavities in upper lobe. Each cavity has a gray, fibrous wall and is surrounded by pale lung parenchyma representing organizing pneumonia.

penetrating trauma, postoperative states, obstruction, hemorrhage or infarction, necrotizing pneumonia, infected emboli, infection of a preexistent cyst or bulla, or extension from nearby infected areas in the mediastinum, chest wall, diaphragm, or infradiaphragmatic locations. Nonaspiration types of pulmonary abscesses of course do not follow the aspiration patterns of distribution, but occur as their coexistent factors dictate. For example, if there is an infarct or an obstructing tumor, infection would occur in the affected areas. Septic emboli are hematogenously spread, and resultant abscesses are often multiple, small, and peripherally distributed (see Fig. 28.29 in Chapter 28).

As aspiration is the principal cause of pulmonary abscess formation, it is reasonable that conditions that favor abscess formation are identical to those favoring aspiration. The locations are similar; men are more frequently affected than women; and the right lung is involved twice as often as the left. The posterior segments of the right upper lobe and superior segments of the right lower lobe are involved most frequently, followed by the corresponding segments on the left side. The single most commonly associated event is an alteration of consciousness; the second most frequent association is poor dental hygiene; and the third is an immunodeficient status.

Poor dental hygiene was noted in cases without other apparent causes of pulmonary abscess in the early studies between 1927 and 1936. The spectrum of bacteria involved in abscess formation is almost identical to that of endogenous oral flora. Moreover children and edentulous older people do not often develop lung abscesses. In children cases caused by aspiration must be separated from other cases of cavitary necrosis, such as pneumatoceles in primary staphylococcal pneumonia.

Anaerobic bacteria are the only organisms cultured in about one half to two thirds of lung abscesses; in the remaining cases either aerobic or facultative aerobic bacteria are isolated, or no bacteria are cultured. The anaerobic bacteria most frequently found are peptostreptococci (i.e., gram-positive anaerobic cocci), pigmented gram-negative bacilli (including bacteroides), and the fusobacteria. Spirochetes were described morphologically in earlier studies and seemed to be significant, as they were present in the growing rims of necrosis; however, they have not been mentioned much recently, perhaps because they are difficult to culture.

About half of cultures with anaerobes also contained aerobic bacteria capable of necrosis, specifically Staphylococcus, Streptococcus, Haemophilus, Pseudomonas, Klebsiella, and Escherichia spp. Patients with predominantly anaerobic pulmonary abscesses often present with indolent symptoms, in contrast to those with necrotizing aerobic abscesses. The latter may be more common in nosocomial-acquired lung abscess. Immunosuppressed patients often acquire gram-negative necrotizing pneumonias and vasoinvasive necrotizing fungal pneumonias, both of which may lead to cavitation. One clue to aspirated bacteria in lung abscesses is finding mixed-
type organisms on smear Gram stain, tissue Gram stain, or culture. The oral cavity abounds with mixed bacteria and is estimated to contain some 200 different types of organisms. This is one reason sputum cultures are notoriously difficult to interpret, and why even oral contamination of a bronchoscope interferes with most lung cultures. Transtracheal and transthoracic needle aspirations, however, correlate well with blood culture results.

The third most frequent factor in abscess formation is host response. Factors that compromise normal host defenses include alcohol ingestion, diabetes mellitus, renal failure, malnutrition, malignancy, and other debilitating factors for any reason. Patients with these factors do more poorly with pulmonary abscesses (and most other insults) than those without.

Pathologically, acute cavities have only a thin transition zone into the reactive adjacent lung parenchyma (see Fig. 5.17B), and do not have the thicker capsules of subacute or some chronic cavities (Fig. 5.18). They show variable numbers of neutrophils and macrophages, along with tissue necrosis. The nearby lung parenchyma has variable findings depending on the rapidity of spread. Rapidly growing cavities necrose nearby lung parenchyma, destroying any early attempts at organization. There may be adjacent hemorrhage, exudate, and fibrin extravasation. In those that are slightly more stable, beginning organization occurs in the surrounding lung parenchyma, along with varying degrees of chronic inflammation outside the areas of acute inflammation (Fig. 5.20A). Collagen becomes deposited at this junction, first as a confluent organizing pneumonia, and later as a capsule (Fig. 5.20B). Blood vessels frequently show variable chronic inflammation and prominent endarteritis obliterans.

Sometimes chronic cavities heal with a thin fibrous border and may retain a coagulum of necrotic debris in their lumen. This apparently indicates that the nearby bronchi have been sealed off. Chronic cavities may resolve by collapse and fibrosis, or may remain open. In the open variety they may become reepithelialized, first with a squamous lining and then with ciliated respiratory lining. In the latter case, the distinction from bronchiectasis or bronchocoele may be somewhat confusing, but multiple bronchial connections in a chronic abscess cavity distinguish these entities.

Spontaneous healing may occur, but healing is greatly aided by appropriate antibiotic dosage. Weiss noted in appropriately treated and monitored cavities that 13% of cavities disappeared by 2 weeks of therapy, 44% by 4 weeks, 59% by 6 weeks, and 70% by 3 months. Surgery is sometimes indicated for nonhealing cavities or when complications develop, such as hemoptysis, persistent sepsis, bronchopleural fistulas, or empyema.

The incidence of abscess formation has greatly decreased during the past 50 years, partly because antibiotics are available and frequently used early in pulmonary infections, and partly because factors leading to
abscess formation are better understood; for example, surgery is avoided with the patient in the upright position or on patients with food in the stomach. In the preantibiotic era approximately 34% of the patients treated either conservatively or by surgery died, and another one third had chronic residual lung disease. More recently the prognosis is much better, but the mortality associated with established abscess formation remains in the range of 25%.

Gangrene of the Lung

Although the term gangrene of the lung has been applied to necrotizing, sometimes putrid, pneumonia in any location, it has more recently been used more specifically to indicate massive necrosis and sloughing of lung associated with severe infection. This entity almost always involves the upper lobes, usually on the right side, and radiographically evolves through typical changes of diffuse infiltrate into multiple cystic spaces that become confluent, leaving a crescent of lung density compressed medially, or occasionally laterally, with a final walled-off area of pus and necrotic lung in an otherwise empty structureless space. Curry and colleagues and Penner et al. attribute the first description of pulmonary gangrene to Laennec in the 1820s. Phillips and Rao, who reported four cases, refer to Sir William Osler's description of diseased lung "converted into a horribly offensive greenish, black mass, torn and ragged in the centre" (Fig. 5.21).

The patients may cough up large pieces of necrotic lung, which in one case was therapeutic. These fragments histologically show ghosts of lung parenchyma and thrombosed vessels. Vasculitis has been described in some reports. Assorted microorganisms cultured from these cases include Klebsiella pneumoniae, Pseudomonas aeruginosa, Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae, and Mucor species. Anaerobic bacteria probably also play a significant role. In their reviews, Phillips and Rao and Penner and colleagues note that similar predisposing factors as those with community-acquired pneumonia, such as aspiration and abscission formation, pertain to this entity, but the location helps distinguish it from the other typical sites of aspiration. When in the upper lobes, it appears to progress through necrotizing pneumonia with thrombosis of arteries (pulmonary and bronchial) and veins.

Although not strictly abiding by the foregoing definition (of localization in upper lobe), in one case total unilateral lung gangrene was attributed to hilar vessel involvement following treatment of a massive hilar recurrence of Hodgkin’s disease. Pulmonary gangrene is life threatening, and surgical removal of necrotic lung tissue is often indicated since only a few patients survive with antibiotic therapy alone.

Lung Torsion

An entire lung, or even one lobe, may rotate around the hilar structures and cause congestion, hemorrhage, or infarction. Cases of torsion involving only single lobes most commonly occur postoperatively when a portion of ipsilateral lung has been removed. Torsion is an infrequent event. A review of the literature in 1994 by Schamaun documented 17 cases of postoperative torsion, five posttraumatic occurrences, and four spontaneous events. In a poll of British thoracic surgeons, however, 35 of 117 responders (30%) had encountered at least one instance of torsion. Torsion has also been documented to occur in transplanted lungs or as a result of pneumothorax or mass lesions. Due to the simultaneous compromise of pulmonary and bronchial arteries and the pulmonary vein, fatal gangrene may occur (see above).
Cholesterol (Endogenous Lipid) Pneumonia

The entity of obstructive, golden, or endogenous lipid pneumonia is most commonly seen secondary to tumor obstruction of large airways, but any of the causes of obstruction can lead to obstructive pneumonia. The obstructive effect accounts for a much larger infiltrate on the usual chest radiograph than is caused by tumor alone. The involved area is primarily supplied by the affected bronchus, and the larger the obstructed bronchus, the greater the area involved. However, even when obstruction occurs in the smallest bronchioles, there may be secondary effects in the centriacinar regions.

Cholesterol crystals may form, and there may be a few lymphocytes and plasma cells. The lipid content of the macrophages accounts for the gross creamy-tan to

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**Figure 5.22.** A. Obstructive pneumonia. Air spaces are filled with finely vacuolated foamy macrophages. There is mild interstitial chronic inflammation. B,C. Comparison of finely vacuolated macrophages in endogenous lipid pneumonia (B) versus large, coarsely vacuolated lipophages in exogenous lipid pneumonia (C). (B,C: same magnification, ×1000.)
golden-yellow color, hence the term golden pneumonia. Obstructed secretions, increased cell breakdown products, and possibly leakage from vessels and interstitium, may give rise to the fat seen in this characteristic reaction. As these products are derived from the lung, this is called endogenous lipid pneumonia. Early in its course the alveolar outlines are well defined though distended with foamy macrophages. If the pneumonia is rapidly reversed, lung function may return. Gradually, permanent damage ensues, including fibrosis and vascular sclerosis, and it is then difficult to restore lung function even though the obstruction may eventually be reversed. Some degree of intraalveolar organization may also be present in approximately 57% of cases. Features of superimposed infection, such as acute inflammation, necrosis, or abscesses are seen in a minority of cases. In contrast to exogenous (aspiration) lipid pneumonia, endogenous lipid pneumonia is characterized by finely vacuolated fat, absence of a foreign-body response, and minimal inflammation and fibrosis of the underlying lung architecture (Figs. 5.15 and 5.22B,C). Sometimes there are changes that suggest pulmonary alveolar lipoproteinosis (see below).

At times parenchymal changes very similar to those just described may be present, although no obstruction of bronchus can be identified, so-called idiopathic cholesterol pneumonia. In 1949, Robbins and Sniffen described 11 cases of chronic nonobstructive cholesterol pneumonia, 10 of which (91%) occurred in men aged 32 to 67 years, the only female being a 12-year-old girl. In extent, five of their cases involved most of the lobe and six cases included a portion of one or more segments, often with pleural adhesions; some had small abscess cavities. The involved areas were wedge-shaped with their bases on the pleura and were described as bright yellow; they were accounted for histologically by abundant, finely vacuolated foamy macrophages, but otherwise these areas presented as mass effects. Mucoid or mucopurulent exudate filled some bronchioles and bronchi, but no other cause of obstruction was present. Bronchiectasis was absent, although focal necrotizing bronchitis was noted. The lobar distribution was not documented. These authors argued against aspiration as they noted the usual aspiration to be more diffuse, often multifocal, and more often seen in lower lobes. Lawler in 1977 summarized the literature on 50 such cases; most were in the age range of 30 to 67 and occurred in men (90%). Most (78%) were in a single location (40% were in the right upper lobe, 18% involved the left upper lobe, and 23% had multifocal involvement).

The clinical, radiographic, and histologic features of idiopathic cholesterol pneumonia overlap those reported by Ackerman et al. and Floyd in chronic organizing pneumonia. Bulmer et al. studying a series of 30 similar cases of unresolved pneumonia, confirmed identifiable foreign material in 11 (37%) and strongly suspected aspiration in another six for a total of 57% in this series. All except two cases (82%) of confirmed aspiration were solitary lesions. It seems reasonable that at least some of both chronic organizing pneumonia and idiopathic cholesterol pneumonia, even when not so confirmed, may be the result of aspiration, usually involving ingredients other than exogenous lipid. Secondary chronic organizing pneumonia, involving large portions of a lobe or presenting as a mass lesion, is not to be confused with the distinctive form of interstitial lung disease termed cryptogenic organizing pneumonia (bronchiolitis obliterans-organizing pneumonia), which is further discussed in Chapter 4.

Fisher et al. have described a series of patients (six children <13 years of age and two adults) with progressive diffuse interstitial lung disease having a combination of histologic features including endogenous lipid pneumonia, interstitial cholesterol granulomas, and patchy alveolar proteinosis (Fig. 5.23). Three patients in this study had severe combined immunodeficiency, two had pulmonary hypertension, and one each had cystic fibrosis (CF), trisomy 10q, and ventricular septal defect (VSD), or lyps uric protein intolerance. All patients exhibited delayed growth, five had digital clubbing, six had depressed appetite or anorexia, five were anemic, and three experienced hemoptysis. Six of eight patients also had evidence of gastroesophageal reflux, which the authors suggest is important in the pathogenesis of this condition. Pulmonary function tests in four patients showed either restrictive or mixed restrictive and obstructive physiology. Chest x-rays predominantly showed nodular pulmonary opacities, while bronchiectasis and perihilar or mild hazy parenchymal infiltrates occurred in one patient each. The mechanism whereby gastroesophageal reflux might elicit this interesting triad of histologic findings is through recurrent microaspiration of gastric content with associated bronchospasm (see discussion of alveolar proteinosis in Chapter 21).

The differential diagnosis of cholesterol pneumonia also includes drug reactions, notably reactions to amiodarone. The clinical history and documentation of amiodarone therapy should facilitate the correct diagnosis (see Chapter 22 and Fig. 22.8). While the foamy macrophages in both of these disorders resemble each other histologically, electron microscopy demonstrates more abundant osmiophilic dense bodies and giant lamellar bodies in many different cell types in amiodarone toxicity compared to similar but smaller inclusions within macrophages in endogenous lipid pneumonia. Compared to endogenous lipid pneumonia, amiodarone toxicity also encompasses a prominent inflammatory response that may include fibrosis, organizing pneumonia and diffuse alveolar damage (see Chapter 22). Other drugs that have been implicated as a cause of endogenous lipid
Atelectasis

Atelectasis is the collapse of aerated lung. Most often it is caused by internal bronchial obstruction of the air flow (absorption atelectasis) (see Fig. 15.2 in Chapter 15), but it may result from external compression of the lung, such as by empyema, mesothelioma, constrictive pleural fibrosis, or tumors, or by internal compression, secondary to a bulla, tumor, or other space-occupying lesions (compressive atelectasis). Pneumothorax is an important cause of atelectasis in the ipsilateral lung. Atelectasis may also be caused by a change in metabolism or surface-wetting balance such as with hyaline membrane disease, ARDS, infection, or gastric acid or other aspiration with loss of pulmonary surfactant. It may also have vascular causes as with embolism, postoperative splinting, obesity (e.g., pickwickian syndrome), or secondary to nerve or muscle dysfunction of diaphragm or chest wall.

Following complete airway obstruction, atelectasis occurs when alveolar oxygen and nitrogen are absorbed. Atelectasis is also commonly seen around chronic inflammatory reactions such as bronchiectasis, and may be part of the sequence of events leading to bronchiectasis (see below). Pathologists must be cautious, however, because most often, when observed histologically, atelectasis is artifactual. Upon the release of negative pressure, air escapes from the lung when the thorax is opened or when lung tissue is excised, and this collapse may cause confusion with preexisting atelectasis (see Fig. 1.2 in Chapter 1).

When bronchial obstruction is partial, it may easily lead to air trapping, as discussed in Chapter 15 (see Asthma). Obstruction of segmental bronchi usually does not cause atelectasis because of preserved collateral ventilation. A collapsed lung may be an isolated cause of fever, but is also a frequent site for superinfections, such as in postoperative patients. Chronic atelectasis may lead to irreversible scarring. The special situation of rounded atelectasis is discussed in Chapter 27 on asbestos-related pathology.

Bronchiectasis

Bronchiectasis simply defined refers to dilatation of bronchi. Included in this broad definition are conditions such as traction bronchiectasis secondary to parenchymal scarring; airway dilatation accompanying parenchymal loss as in emphysema; or reversible dilatation, which may be seen radiographically in atelectasis or pneumonia.
TABLE 5.1. Causes of localized bronchiectasis

A. Bronchial obstruction
   1. Neoplasm
   2. Aspirated foreign body (pseudosequestration)
   3. Broncholith
   4. External compression (lymphadenopathy) (middle lobe syndrome)
   5. Allergic bronchopulmonary aspergillosis

B. Infection
   1. Tuberculosis
   2. Necrotizing bacterial/viral infections

C. Gastric acid aspiration

D. Traction bronchiectasis

A more selective definition of bronchiectasis, and the type usually understood by pathologists, is irreversible fixed airway dilatation associated with inflammation and destruction of bronchial matrix components. Bronchiectasis can be further categorized as localized or diffuse/multifocal. Causes of localized bronchiectasis, the most important of which is airway obstruction, are listed in Table 5.1. Localized bronchiectasis may also have an infectious etiology, most notably pulmonary tuberculosis (see Fig. 9.13 in Chapter 9).

Obstructive bronchiectasis is most commonly seen beyond endobronchial tumors (Fig. 5.24), but foreign bodies, concretions such as broncholiths, secretions such as inspissated mucus in mucoid impaction and allergic bronchopulmonary aspergillosis (see Chapter 15), strictures, or compression as by tumor or enlarged nodes may play a role. Rarely, lack of cartilaginous support with airway collapse, bronchial atresia, or mucosal webs may be associated with bronchiectasis. Obstructive bronchiectasis occurs anywhere obstruction occurs, but there are some localizing factors in a few of these conditions: the upper lobe in allergic aspergillosis or with primary epithelial tumors, which are more common in this site; the middle lobe with its tendency toward airway compression (middle lobe syndrome); and localized bronchiectasis governed by the usual routes of aspiration (covered earlier in this chapter). There are many exceptions, and bronchoscopy is usually indicated in both children and adults to diagnose the type of obstruction. Localized bronchiectasis is often successfully treated by surgical resection or elimination of the cause of bronchial obstruction.

Diffuse or multifocal bronchiectasis is usually of the nonobstructive type, the major causes of which are listed in Table 5.2. It is this type that is more frequently a cause

FIGURE 5.24. Obstructive bronchiectasis, distal to a slowly growing carcinoid tumor, occupies large portion of the upper lobe.

TABLE 5.2. Major causes of diffuse or multifocal bronchiectasis

A. Infection
   1. Mycobacterial
   2. Respiratory infections of childhood
      a. Bacterial (e.g., pertussis)
      b. Viral (e.g., adenovirus, respiratory syncytial virus, measles)
   3. Bronchiolitis obliterans syndromes
      a. MacLeod’s (Swyer-James) syndrome
      b. Diffuse panbronchiolitis

B. Idiopathic (presumed infectious)

C. Hereditary diseases
   1. Cystic fibrosis
   2. Primary ciliary dyskinesia
   3. Young’s syndrome
   4. α1-Antitrypsin deficiency

D. Congenital bronchiectasis
   1. Williams-Campbell syndrome
   2. Tracheobronchomegaly (Mounier-Kuhn)

E. Immunodeficiency
   1. Hypogammaglobulinemia
   2. HIV disease
   3. Lung transplant
   4. Other immunodeficiency disorders

F. Allergic bronchopulmonary aspergillosis

G. Collagen vascular diseases
   1. Rheumatoid arthritis
   2. Sjögren’s syndrome
   3. Other (rare)

H. Inflammatory bowel disease
   1. Ulcerative colitis
   2. Crohn’s disease (rare)

I. Chemical injury/aspiration
   1. Toxic fume inhalation (SO2, NO2, H2S)
   2. Gastric acid aspiration
   3. Heroin abuse
of significant chronic obstructive pulmonary disease (COPD) and respiratory failure. Nonobstructive bronchiectasis occurs most frequently in the basal segments of the lower lobes, often sparing the superior segment and the anterior basal segment. It is found more than twice as frequently in the left lower lobe as in the right.\textsuperscript{175-177} Next in frequency are the right middle lobe and its counterpart, the lingula. These areas of the lung may have the poorest drainage. The upper lobes may be involved but are usually not solely involved by nonobstructive bronchiectasis. Tuberculosis more selectively causes bronchiectasis in the upper lobes, and cystic fibrosis should be considered in cases of upper lobe involvement without a definitive etiology. About one third of the cases of nonobstructive bronchiectasis have bilateral involvement.\textsuperscript{176,178,179}

Macroscopically bronchiectasis typically involves the second to the eighth order of segmental bronchi, sparing the larger, more proximal airways, which are protected by a firmly supporting cartilaginous network.\textsuperscript{179-181} More distal airways are often obliterated or effaced as the number of bronchial divisions is reduced (Fig. 5.25).\textsuperscript{173,182} Within a bronchopulmonary segment there may be patchy involvement (see Fig. 1.9 in Chapter 1). There is also apparent loss of more distal lung parenchyma as the dilated airways approach the visceral pleura (Fig. 5.25).\textsuperscript{173,182}

Bronchiectasis has been divided into many different patterns grossly and radiographically. The most widely applied classification is that suggested by Reid\textsuperscript{182}: (1) saccular (cystic), (2) cylindrical (fusiform or tubular), and (3) varicose. In the saccular form, the distal extensions of the bronchi are more dilated than proximal portions, described by Reid as “globular ballooning.” Usually, the second- to fourth-order bronchi are involved. Cylindrical bronchiectasis consists of evenly enlarged tubular dilatation of bronchi, usually involving the sixth- to eighth-order bronchi.\textsuperscript{183} On bronchograms dilated bronchi come to an abrupt, square-ended termination thought to be caused by impacted endobronchial secretion.\textsuperscript{173} The varicose type describes focal dilatation separated by more narrow areas (see Fig. 1.9 in Chapter 1). These various gross patterns were previously best visualized by bronchography, and are not specific for any given etiology, although certain clinical-pathologic correlations have been made (see below).

Whitwell\textsuperscript{175} integrated histologic features into his classification of follicular, saccular, and atelectatic bronchiectasis. Follicular bronchiectasis most frequently begins in childhood as the sequela of viral infections, most notably adenovirus.\textsuperscript{183} Saccular bronchiectasis, in Whitwell’s series, was often found to be postinfective or idiopathic. The pathogenesis of atelectatic bronchiectasis was linked to lobar bronchial obstruction, often by enlarged lymph nodes. Congenital bronchiectasis, purportedly due to cartilage deficiency in the bronchial walls, is a controversial entity discussed elsewhere in this chapter under the Williams-Campbell syndrome.\textsuperscript{180,181,184} Not to be confused with congenital bronchiectasis are those hereditary conditions, such as cystic fibrosis or primary ciliary dyskinesia, that predispose to the subsequent development of progressive bronchiectasis (see below).\textsuperscript{174,180}

Patients with bronchiectasis typically present clinically with forceful cough, purulent sputum production, wheezing, and recurrent pneumonia in the bronchiectatic zones. Wet bronchiectasis refers to abundant inflammation and mucus hypersecretion, whereas dry bronchiectasis refers to minimal sputum production. Dry bronchiectasis is most common in the upper lobes, is often of the cylindrical type, and probably relates to better drainage in this zone. Hemoptysis commonly presents as blood-streaked sputum, but may be massive and life-threatening. Frequently purulent sinusitis accompanies bronchiectasis and may contribute to its development. The chest radiograph is usually abnormal in bronchiectasis, including specific features of ring-like shadows due to dilated airways seen on end, or of tram lines when the airways are visualized longitudinally.\textsuperscript{185} High-resolution CT scan is the best current modality for diagnosing bronchiectasis, revealing airways that are dilated relative to the adjacent blood vessels, lack of airway tapering, constrictions along the path of the airway, and terminal balloon-like cysts.\textsuperscript{185,186} Pulmonary function tests show obstructive changes with reduced forced expiratory volume in 1 second (FEV\textsubscript{1})/
forced vital capacity (FVC) and frequently airway hyperresponsiveness.\textsuperscript{185} Various theories have been proposed to explain non-obstructive bronchiectasis. Inflammation seems to best account for the changes that are observed, including the fact that the involved zones of lung are those most difficult to drain. It was known even in the 1930s and confirmed in subsequent decades that respiratory infection often preceded bronchiectasis.\textsuperscript{175,176,187–190} Usually older children and young adults have the well-developed disease pattern, but also have a history of infections before the age of 2 or 3 years, with recurrent respiratory problems dating from this time.\textsuperscript{187} Many patients may appear stable and do well for some time, and then develop a progressive course of recurrent infections and systemic toxicity.\textsuperscript{174,177–182,187–200} In approximately 50% of cases of bronchiectasis, however, a specific inciting factor is not identified—so-called idiopathic bronchiectasis.\textsuperscript{195} In these patients, childhood respiratory infections especially those likely to have produced bronchiolitis obliterans, are presumed to have initiated the process of bronchiectasis.\textsuperscript{173,195,196}

Viral infections may be important in many cases.\textsuperscript{167,174,196–203} Glauser and associates\textsuperscript{204} noted in an extensive review that measles and pertussis immunizations probably have played a significant role in decreasing the incidence of bronchiectasis. Bacteria also play a significant role, both in primary infections (see following) and in superinfections or reinfections in areas of previous injury. Aggressive treatment of pediatric pulmonary infections with antibiotics has helped to make bronchiectasis a disappearing disease.\textsuperscript{204} Historically, the impact of immunizations and antibiotics on the declining incidence of bronchiectasis occurred at about the same time, and it is difficult to differentiate their effects; nonetheless, this association supports the role of early infection in initiating bronchiectasis.

Excluding cases of Kartagener’s syndrome, the concurrence of sinusitis and bronchiectasis is greater than expected. As early as 1929, Quinn and Meyer\textsuperscript{20} noted a 58% incidence of chronic sinusitis in cases of bronchiectasis. Aspiration of infective material from the sinuses may play a role. However, another study noted a 15% incidence of sinusitis in cases with less than 5 years of symptoms of bronchiectasis compared to the 44% incidence in all cases of bronchiectasis.\textsuperscript{179} \textit{H. influenzae}, a common pathogen of the upper respiratory tract, is also found with some regularity in lung cultures from patients with bronchiectasis. Anaerobic bacteria, reflecting endogenous oral flora, may also be cultured from bronchial secretions. Long-term antimicrobial treatment may be required for complete eradication of these organisms.

The role of recurrent infection in perpetuating and aggravating bronchiectasis cannot be overemphasized. This has been documented in children and adults. The dilatations of the bronchial contours, their irregularities, their relative stenosis at the proximal end, altered secretions and exudate, surface mucosal ulcerations, and metaplasia all play a role in hampering adequate drainage. A vicious cycle ensues as the injured area perpetuates further injury, leading to increased damage and progressive bronchiectasis.

Necrotizing inflammation involves bronchial walls and adjacent parenchyma (Fig. 5.26). Some scarring probably

\textbf{Figure 5.26.} Diagram of role of infection in formation of bronchiectasis. \textbf{A.} Infection involves areas adjacent to bronchi and more distal connections. \textbf{B.} With resolution and scarring, involved areas contract and pull against bronchi and cause their dilatation and overall lung contraction (dotted line). (Courtesy of A.A. Liebow Pulmonary Pathology collection, San Diego, California.)
takes place in healing, with retraction of surrounding tissue. Retraction occurs circumferentially, and bronchial dilatation results. As noted, the more distal bronchi and bronchioles are often destroyed. There is also general lung contracture due to atelectasis of involved zones, while nonaffected lobes may undergo compensatory hyperinflation (Fig. 5.26). The basic principles of fibrosis and contraction also apply to traction bronchiectasis seen in interstitial fibrosis and honeycombing. Traction bronchiectasis is usually not as marked as primary bronchiectasis, and is localized and most severe in the peripheral subpleural zones where fibrosis is often most prominent (see Chapter 19).

Grossly, the involved lung tissue is usually atelectatic, gray-blue, shrunken, and rubbery. There may be zones of golden or obstructive pneumonia, and sometimes these zones form layers around the dilated bronchial tubes. It may be difficult or impossible to adequately inflate such a chronically contracted specimen. The involved bronchi are dilated instead of following their smoothly contoured courses as they extend peripherally. These dilated bronchi almost reach the pleural surface and run in a somewhat parallel or radial fashion without interbronchial connections (Figs. 5.25 and 5.26). Partially or totally circumferential thin folds in the mucosa extend internally from the wall and are seen as transverse infolded pleats on the bronchial cast (see Fig. 1.9 in Chapter 1). These give the appearance of webs or bands of mucosa. There are variably sized outpouchings, larger ones between the remnant bronchial cartilages, and dilated smaller pits that appear to be dilated submucosal glands. Grossly, elastic fibers can be seen still running through the wall, but these are more widely separated than is normal because of the stretched diameter of the bronchus. In wet bronchiectasis there is thickening of the wall, and mucinous, granular, semisolid material accumulates within the lumen (Fig. 5.27). Occasionally this material hardens and even calcifies (see broncholithiasis, below). In dry bronchiectasis the wall is thin, almost translucent, and gray-pink without mural thickening.

Microscopically the respiratory mucosa may be intact, show squamous metaplasia, or be ulcerated or inflamed (Fig. 5.28). The bronchial walls are usually chronically inflamed. Submucosal glands and surface goblet cells are not prominent and may decrease, although they may occasionally increase. Elastic tissue is preserved except in areas of necrosis (Fig. 5.28). Smooth muscle is usually present and often shows some degree of hypertrophy; occasionally this is atrophic. Cartilage seems less obvious and occasionally is eroded, but most often appears normal histologically. In advanced saccular bronchiectasis cartilage is markedly reduced or absent. Neutrophils, macrophages, and desquamated and mucinous debris are present in the bronchial lumen in wet bronchiectasis. Acute inflammatory cells may infiltrate the bronchial wall or the adjacent lung parenchyma depending on the status of inflammation and active infection at the time of lung removal. As these patients are subject to recurrent infections, acute pneumonia may also be present.
FIGURE 5.29. Follicular bronchitis/bronchiectasis. Lymphoid follicles appear to constrict bronchial lumens.

Lymphocytes and plasma cells usually predominate in bronchial wall and surrounding lung tissue. In follicular bronchiectasis, hyperplastic lymphoid follicles may appear to constrict the bronchial lumens (Fig. 5.29). There may be a degree of obstructive pneumonia correlating with the gross yellow color. Small granulomas are present in a few cases, apparently as a reaction to inspissated material within the bronchi. If granulomas are extensive or present in the adjacent lung parenchyma, in more normally contoured segmental and subsegmental bronchi, or in lymph nodes, one must consider fungal or mycobacterial infections. If granulomas are confined to the injured areas, one must also consider aspiration. Bronchioles are often constricted or obliterated beyond the dilated bronchi (Fig. 5.30). Other small airways may be dilated and sometimes mucus-filled probably because of their obstruction at the junction with the larger bronchi. Foci of carcinoid atypical proliferation (tumorlets) occur with some frequency in bronchiectasis (see Chapter 36). Bronchial arteries respond to sustained inflammation, and may exceed 1 mm in diameter. Ulceration of these systemic arteries accounts for the bright-red appearance of hemoptysis.

Middle-Lobe Syndrome

The right middle lobe and occasionally its left-sided counterpart the lingula, have lobar bronchi that branch from their parent supply at a more acute angle than most other dividing bronchi (see Chapter 2). The middle lobe bronchus is relatively narrow, and there are frequently moderately prominent nodes in the angle of bifurcation that may compress and further constrict the bronchus. The subcarinal node may even approach this angle. Several authors have also suggested there is less effective collateral ventilation in the middle, compared to the adjacent upper lobe. Because of these anatomic characteristics there is a greater tendency toward middle lobe and lingular atelectasis, inflammation, nonspecific scarring, broncholith formation, and bronchiectasis—collectively termed middle lobe syndrome (MLS). In addition to peribronchial lymphadenopathy, MLS can result from numerous disorders including asthma, tuberculosis, foreign bodies, CF, broncholiths, endobronchial silicosis, cardiovascular and
TABLE 5.3. Pathologic findings in 21 patients with middle lobe syndrome

| Pathologic Findings                                             | No.* |
|-----------------------------------------------------------------|------|
| Airways (bronchi, bronchioles)                                  |      |
| Bronchiectasis                                                  | 10   |
| Bronchiolitis with lymphoid hyperplasia (“follicular bronchiolitis”) | 7    |
| Organizing pneumonia                                            | 6    |
| Broncholithiasis                                                 | 1    |
| Distal air spaces, interstitium                                 |      |
| Atelectasis                                                     | 5    |
| Granulomatous inflammation                                      | 5    |
| Necrotizing granulomas (positive acid-fast bacillus [AFB] stains in three; M. avium-intracellular complex cultured in two) | 3    |
| Nonnecrotizing granulomas (M. fortuitum cultured in one; sarcoidosis in one) | 2    |
| Abscess                                                         | 4    |
| Hemosiderin pigment                                             | 3    |
| Interstitial fibrosis                                           | 2    |
| Honeycomb change                                                | 1    |
| Pleura                                                          |      |
| Fibrosing pleuritis                                             | 3    |

* Some patients had more than one pathologic finding.

Source: Kwon et al.212 Copyright 1995, with permission from Elsevier.

bronchopulmonary malformations, and allergic bronchopulmonary aspergillosis.211-213

The pathologic findings in resected lung specimens of 21 patients with middle lobe syndrome have been comprehensively described most recently by Kwon and colleagues,212 and are delineated in Table 5.3. Although the histologic findings are nonspecific, a combination of bronchiectasis, bronchiolitis, and atelectasis is typical.212 In this series, a mechanical obstruction (broncholith) was identified in only one patient.212 As early as 1966, Culinier208 also recognized bronchial patency in most cases of middle lobe syndrome. The current understanding suggests that MLS is due to recurrent infection related to poor lung drainage, possibly associated with intermittent obstruction of the precariously situated bronchi in the setting of reduced collateral ventilation of the middle lobe.208,212

**Broncholithiasis**

Broncholiths represent calcified material in the airways.214-220 They most commonly are calcified lymph nodes that compress bronchi and either partially or completely erode through the bronchial walls (Fig. 5.31).217,221 They then may be expectorated (lithopytis) (Fig. 5.32)
or aspirated and cause hemorrhage or obstructive changes, including cough, atelectasis, pneumonia, abscess formation, bronchiectasis, or air trapping. Broncholiths form less often from chronic reaction to retained aspirated material or eroded fragments of calcified or ossified bronchial cartilage. They may also occur with retained mucus as in bronchiectasis. Historically, “spitting stones” dates back to descriptions by Aretaeus, Galen, and Aristotle. Although usually less than 1 cm in diameter, a record-sized calculus of 139 g (1/4 lb) occurred in a patient who also had produced multiple sand-like or melon-seed-sized calcified particles. The latter two organisms probably represent superinfections of necrotic debris. Silicotic lymph nodes (see Chapters 36 and 40). Fibrocaseous lymph node lesions. The outer surface of the dia. The latter two organisms probably represent superinfections of necrotic debris. Silicotic lymph nodes may also cause a similar reaction. Men and women are about equally affected, and although calcified nodes may occur at any junction of the bronchial tree, they are 2 to 6.5 times as common on the right side, and favor the anterior superior segment of the upper lobe and the bronchus intermedius, along with the right middle lobe bronchus, where they may produce the middle lobe syndrome. The superior segment of the lower lobe is also a site of occurrence. Occasionally, erosive calcified nodes may cause bronchopleural fistulas and are the most common cause of bronchoesophageal fistulas. Retraction diverticula of the esophagus may also occur secondary to peribronchial fibrosis and calcified mediastinal lymph nodes associated with broncholiths.

Calciﬁed nodes have also been studied with CT scans. In the retrospective series by Conces et al., of 15 patients with CT-proven broncholiths, 11 (73%) had juxtabronchial calcified nodes identified on chest radiographs. Calcified intraparenchymal nodules were seen radiographically in only four (27%) patients. Bronchoscopy is less accurate in detecting calcifications, ranging from 28% to 56% of cases. Rarely, calcifying tumors such as an ossifying bronchial carcinoma or endobronchial hamartoma can cause confusion (see Chapters 36 and 40).

Histologically broncholiths appear similar to calcified fibrocaceous lymph node lesions. The outer surface of the often sharp-edged calculus may be coated with inﬂammatory exudate or, in cases of actinomyces superinfection, eosinophilic rays (Splendore-Hoeppli phenomenon). The GMS stain may disclose histoplasma yeast forms in the centrally necrotic area of the calculus.

Within the chest, fistulas may be bronchopleural, bronchocutaneous, bronchomedialstinal, or bronchoesophageal in their connections. An aortobronchial fistula is a rare (and often fatal) complication of previous aortic or cardiac surgery. Bronchopleural fistulas are the most common form and often are secondary to surgery, such as from a leaking postoperative bronchial stump. Other causes include necrotizing pneumonia or abscess, penetrating wounds, eroding granulomatous disease, penetrating broncholiths, or malignancies. See Chapter 6 for congenital causes. Extrapulmonary bronchial fistulas include connections with bile ducts, pancreas, and other assorted sites.

Bronchial Mucocele—Bronchocele—Bronchial Atresia

Bronchocele means one or more dilated bronchi filled with fluid, which may be mucinous (bronchomucce) or purulent (bronchopyocele). This condition is caused by stenosis or occlusion of the proximal end of dilated sac(s), and therefore differs from bronchiectasis and mucoid impaction, in which proximal ends are generally still patent. It may be either congenital, or early or late acquired, usually of postinflammatory nature but sometimes of malignant nature. Localized emphysema, which occurs around the bronchocele, may be caused either by inflammation early in lung growth with continued traction-type effects on nearby lung, or by sustained air-trapping due to airway obstruction. Many cases are reported as bronchial atresia. Bronchocele/ atresia may present in adults or children and typically affects the left upper lobe. A characteristic CT appearance is that of a branching mass surrounded by hyperlucency. An irregularly cylindrical (sometimes branched) thin-walled cyst (Fig. 5.33A) grossly and histologically resembles a bronchocele lined by respiratory or squamous epithelium. Occasionally a scar or intrabronchial web proximal to the lesion represents the remnant atretic or occluded bronchus. The adjacent bronchial arteries may appear hypertrophic, especially if there have been recurrent infections (Fig. 5.33B).

Bronchocoele may be a relative of saccular bronchiectasis and may be the etiology for some so-called intraparenchymal bronchogenic cysts (see below and Chapter 6). Mucoid impaction may also be related to an allergic effect, often to noninvasive Aspergillus (see Chapter 15), usually does not have proximal bronchial stenosis occlusion, and has more eosinophils and cellular debris in the mucus, in addition to intraluminal hyphae. Bronchocele/ atresia is distinguished from intralobar seques-
5. Aspiration, Bronchial Obstruction, Bronchiectasis, and Related Disorders

FIGURE 5.33. Bronchial atresia/mucocele. A. Ovoid, smooth-walled cyst terminates blindly near the hilum (scale equals 3 cm). B. Pulmonary artery (PA) is overshadowed by prominent, hypertrophic bronchial arteries (BA). Lumen of cyst is at top (Movat stain).

Bronchogenic Cysts

Bronchogenic cysts are closed sacs lined by respiratory mucosa, usually with bronchial glands, smooth muscle, and cartilage in their walls. They often represent congenital fragments that drop off or are remnants of the original budding of the lungs from the primitive endodermal canal. They are most common in the middle mediastinum where they account for 10% to 15% of all primary mediastinal masses but can be seen as isolated mass(es) in the lung. Within the lung, some may form as bronchoceles as discussed previously. A series of 86 cases of bronchogenic cyst, with 66 (77%) in the mediastinum and 20 (23%) in the lung, was presented by St. Georges et al.248 from Montreal. A similar distribution was recorded in adult patients by Patel and colleagues.249 Of interest, 75% to 90% of those in the lung were symptomatic at the time of operation, most often because of infection or bronchial obstruction.248,249 Although suspected, a preoperative diagnosis was not correctly made in any case in the large Montreal series.248 The presence of bronchial epithelial cells on transbronchial fine-needle aspiration (FNA) was found not to be specific for the diagnosis of bronchogenic cyst.249 Most occur in the lower lobes, but all lobes may be affected.248-250 The CT appearance is that of a well-defined ovoid lesion, with surrounding mosaic and band-like linear attenuation consistent with emphysema and bronchiolar metaplasia/fibrosis.250 A bronchioloalveolar cell carcinoma arising in a bronchogenic cyst in a 37-year-old woman has been reported as a rare association.251 Bronchogenic cysts are uncommon in adults and are further discussed in children in Chapter 6.

Bronchorrhea

Bronchorrhea is arbitrarily defined as production of more than 100 mL of sputum per day.252 Although it is a clinical symptom, pathologists may ponder the differential diagnosis if faced with this history on a specimen request card. Bronchorrhea may be idiopathic, or secondary to chronic bronchitis, bronchiectasis, scleroderma, asthma, mucinous bronchioloalveolar carcinoma, metastatic mucinous adenocarcinoma, tuberculosis, or relapsing polychondritis.252-258 Cytology exams, cultures, or transbronchial biopsies may help evaluate at least some of these possibilities.

Cystic Fibrosis

Cystic fibrosis is a prototypic example of bronchocentric inflammation and bronchiectasis and the most common lethal genetic disease among Caucasians, having a frequency of approximately 1 in 2500 live births.259-261 The
molecular defect of this autosomal recessive disorder was discovered in 1989 to involve mutations in a 1480 amino acid polypeptide, the cystic fibrosis transmembrane conductance regulator (CFTR), encoded by a gene on the long arm of chromosome 7. Over 1000 different mutations of the CFTR gene have so far been identified, but the most frequent mutation worldwide and the most severe genetic lesion, is the deletion of phenylalanine at position 508 of CFTR (AF508), accounting for over 70% of affected patients.

Cystic fibrosis transmembrane conductance regulator functions as a cell membrane-associated, cyclic adenosine monophosphate (cAMP)-regulated chloride channel, which also has regulatory activity on the absorption of sodium through a separate epithelial channel (ENaC). The structure of CFTR is schematically depicted in Figure 5.34. Mutations in CFTR have been grouped into six major types, each of which may present phenotypically as CF: (1) lack of synthesis of CFTR; (2) defective processing of CFTR such that it does not reach the cell membrane; (3) aberrant regulation of ion transport due to dysfunctional CFTR; (4) abnormal conductance of chloride ions; (5) partly defective production and processing; or (6) accelerated turnover at the cell surface (Fig. 5.35). The AF508 mutation is a type 2 defect in which abnormal CFTR is sequestered within cellular organelles leading to reduced insertion into the cell membrane, markedly limiting the ability of chloride to cross the membrane. In epithelial cells of bronchi, biliary tract, and intestine, impaired transport of intracellular chloride and its accompanying water molecules leads to dehydration of ductal and lumen secretions. In bronchial epithelium there is also enhanced intracellular absorption of sodium ions, which further dehydrates secretions within the airway lumen. In contrast, the uptake of extracellular chloride is inhibited in sweat ducts, causing an elevation of sweat chloride concentration, a key diagnostic indicator of CF. It has long been recognized that patients with CF are predisposed to lung infection. Current hypotheses suggest that susceptibility to infection may be related not only to entrapment of bacteria in thick bronchial secretions, but also possibly to abnormal binding observed shortly after the neonatal period and is the most important cause of morbidity and mortality.
and reduced uptake of bacteria by epithelial cells, or impaired epithelial antimicrobial protection provided by defensins (natural antibiotics of the innate immunity system).\textsuperscript{259,283-289} Even in infants without apparent infection, however, bronchoalveolar lavage studies document ongoing bronchial inflammation associated with increased levels of endobronchial IL-8, a potent cytokine that recruits neutrophils into the inflammatory response, and relatively decreased levels of IL-10, an inhibitor of proinflammatory cytokines.\textsuperscript{284-294} It is as yet undetermined whether or not intrinsically exaggerated inflammatory responses are the direct result of mutations in CFTR.\textsuperscript{295}

Infection and inflammation stimulate bronchial mucus secretion leading to a vicious cycle of worsening airway infection and obstruction, progressing to chronic bronchitis, bronchiolitis obliterans, and bronchiectasis.\textsuperscript{286} The chronic pulmonary complications of CF evolve from the airway disease.\textsuperscript{277} Hyperinflation or collapse is the direct result of bronchial obstruction. Air trapping and postinflammatory cystic lesions underlie an increased susceptibility to recurrent pneumothorax. Pulmonary hypertension and cor pulmonale derive from sustained hypoxia, while hemoptysis is a direct effect of bronchiectasis and bronchial artery hypertrophy.\textsuperscript{277}

Endobronchial infection tends to occur in sequential fashion, initiated by \textit{S. aureus}, followed by \textit{H. influenzae}, and finally by \textit{P. aeruginosa} (mucoid strains).\textsuperscript{260,288} Once initiated, pseudomonas infection is nearly impossible to eradicate. Airways at all levels become impacted with degenerating neutrophils, mucus, basophilic strands of DNA, and bacteria.\textsuperscript{286,296} Epithelial injury is accompanied by basal cell hyperplasia.\textsuperscript{297} Proliferating basal cells have uniform Ki-67 immunostaining and express basal cell cytokeratins (CK5/14) and epidermal growth factor receptor.\textsuperscript{299} In the central bronchi, squamous metaplasia and goblet cell hyperplasia, respectively, impede airway clearance and contribute to mucous secretion. Ultrastructurally, however, respiratory cilia are either normal or mildly altered by nonspecific degenerative features.\textsuperscript{298,299} Submucosal glands are enlarged and chronically inflamed behind ducts that are obstructed by dense, inspissated, eosinophilic secretion (a characteristic, but not pathognomonic feature of CF) (Fig. 5.36).\textsuperscript{300-302} Although bronchial smooth muscle in individual patients may appear hypertrophic, its mean volume density is within the normal range.\textsuperscript{300}

In patients with CF-associated lung disease, saccular bronchiectasis is usually present beyond 4 months of age.\textsuperscript{276} Although all bronchopulmonary segments may be affected, bronchiectasis tends to be more severe in the upper lobes (Fig. 5.37).\textsuperscript{301,303,304} Blind-ended ectatic airways, devoid of cartilage, are surrounded by alveolar, chronically inflamed, and fibrotic parenchyma (see Fig. 5.27).\textsuperscript{296} Bronchial mucosa is frequently denuded or

**Figure 5.35.** Schematic representation of five major classes of CFTR gene mutations in CF. The class VI defect is not depicted in the figure (refer to text). (Modified from Moss,\textsuperscript{268} with permission.)
ulcerated leaving the bronchial surface lined by highly vascular granulation tissue that is rich in histiocytes (see Fig. 5.28). In severe disease, bronchi terminate in large, juxtapleural, thin-walled cavities that present radiographically as contiguous, bubble-like cysts. Intrapleural blebs or emphysematous bullae are less common forms of cystic lesions, which contribute to an increased incidence of pneumothorax. Extensive acute and chronic bronchiolitis and broncholar mucoid impaction impart a finely nodular texture to the parenchymal surface and account for a micronodular radiographic appearance (Fig. 5.38). Bronchiolitis obliterans, predominantly of the constrictive type, contributes importantly to airway obstruction, and likely precedes the development of bronchiectasis (see Fig. 5.30). Occasionally, occlusion of respiratory bronchioles by polypoidal protrusions of fibroblastic tissue accompanies interstitial and organizing pneumonia. Small airway density decreases with age and is most significantly reduced in patients with hypercapnia.

The lung parenchyma is grossly indurated by multifocal, bronchocentric chronic pneumonia and fibrosis, with features of both organizing pneumonia and endogenous lipid (cholesterol) pneumonia. A variable degree of acute bronchopneumonia may also be seen at autopsy. Some patients who are colonized by *Burkholderia cepacia* undergo an accelerated decline due to acute necrotizing pneumonia (see Figs. 8.61 and 8.62 in Chapter 8). Other patients colonized by *Burkholderia* follow a more protracted course, similar to those colonized by *P. aeruginosa*. Fungi and nontuberculous mycobacteria may also colonize CF airways and contribute to lung destruction. Bhargava and colleagues identified fungal
organisms histologically in 21% of CF patients retrospectively studied at autopsy. The dilated, obstructed airways of CF patients are predisposed to fungal colonization, accounting for an increased prevalence of allergic bronchopulmonary aspergillosis (ABPA) of approximately 2.0%.318 Infrequently the pathologic features of ABPA, including bronchocentric granulomatosis, are superimposed on chronic CF-associated airways disease (see Fig. 15.19 in Chapter 15).277 In CF patients with nontuberculous mycobacterial infections (often due to Mycobacterium avium or rapidly growing strains like M. chelonae or M. abscessus), necrotizing fibrocaseous granulomas may be present.315,316,319,320 Pulmonary lesions are most likely to be found in patients with repeatedly positive sputum cultures for mycobacteria (see Chapter 9).320

The pulmonary vascular changes of CF-associated lung disease are usually pronounced. Chronic hypoxia and inflammatory changes contribute to pulmonary artery medial hypertrophy and intimal fibrosis of muscular pulmonary arteries and medial myxoid degeneration of elastic arteries.321-326 Postmortem arteriograms often show abnormally tapered arteries with a reduced background haze (see Fig. 1.8 in Chapter 1).277 Morphometric studies provide evidence of a decreased density of arteries, which correlates inversely with the degree of right ventricular cardiac hypertrophy.321 The dropout of arteries may be related to impaired postnatal growth or to vascular destruction secondary to chronic hypoxia or sustained inflammation.321 Right ventricular cardiac hypertrophy, seen at autopsy in approximately 84% of CF patients older than 3 years of age, is a direct consequence of pulmonary artery remodeling and associated pulmonary hypertension.321

Bronchial arteries also undergo significant hypertrophy as a response to sustained bronchial inflammation, bronchiectasis, and bronchocentric abscesses (Fig. 5.39).327-329 The source of hemoptysis in CF patients is most frequently the delicate capillaries within airway granulation tissue (see Fig. 5.28).330,331 Occasionally, mucosal ulcers erode into hypertrophied bronchial vessels leading to life-threatening massive hemoptysis (Fig. 5.39). Interventional bronchial artery embolization of metal coils, polyvinyl alcohol (Ivalon), or Gelfoam particles is undertaken to induce thrombosis and control bronchial artery bleeding.331,332 Degenerated remnants of embolized polyvinyl alcohol may surround stenotic or occluded bronchial arteries in patients who have undergone this procedure.333 Bronchopulmonary arterial anastomoses may further allow the paradoxical entry of small embolized particles into the pulmonary arterial circuit (see Fig. 28.42 in Chapter 28).334

Other less frequently reported complications of cystic fibrosis include systemic amyloidosis, intralobar sequestration, and anaerobic lung abscess.335-338 Emphysema is usually a minor feature, localized to bronchiolocentric scars or as paraseptal emphysema in the upper lung zones.278,305,329 Cystic fibrosis patients with indwelling venous access devices may surreptitiously inject aqueous suspensions of psychoactive pharmaceutical tablets leading to pulmonary artery obstruction due to embolized tablet filler materials (see Chapter 26).339

Figure 5.39. Cystic fibrosis. A. Postmortem arteriogram. Prominent tortuous bronchial arteries (BA) run adjacent to pulmonary arteries (PA). B. Crowded hypermuscular, “dystrophic” bronchial arteries, adjacent to bronchial cartilage.
Primary Ciliary Dyskinesia

Primary ciliary dyskinesia (PCD) is an autosomal recessive disorder, occurring in approximately 1 of 15,000 to 30,000 persons, characterized by the absence or dysregulation of ciliary movement mainly due to ultrastructural defects in the ciliary axoneme. (see Chapter 2).\textsuperscript{340-344} Cilia on the respiratory epithelial surface play an important role in propelling mucus, bacteria, and inhaled particulate debris out of the lung (see Chapter 3). As a result of impaired clearance due to ciliary malfunction, patients with PCD are predisposed to chronic sinusitis, serous otitis, and recurrent bronchopulmonary infections beginning in early childhood.\textsuperscript{345,346} Primary ciliary dyskinesia has also been implicated as a cause of neonatal respiratory distress syndrome.\textsuperscript{347,348} Male patients are usually infertile due to poor flagellar motility of sperm.\textsuperscript{345} Approximately 50% of patients with PCD also have situs inversus secondary to abnormal rotation of embryonic epithelia consequent to the lack of ciliary movement.\textsuperscript{343} The syndromic triad of situs inversus, sinusitis and bronchiectasis was first proposed by Kartagener in 1933, and is now designated Kartagener’s syndrome (Fig. 5.40).\textsuperscript{349,350} While PCD is an important cause of bronchiectasis, the prognosis is generally more favorable than that of CF.\textsuperscript{340}

In 1976 Afzelius\textsuperscript{340} and Pedersen and Mygind\textsuperscript{341} were among the first to recognize that ultrastructural abnormalities of ciliary dynein arms were associated with Kartagener’s syndrome. Originally termed immotile cilia syndrome by Afzelius, it is now recognized that there are numerous structural variations that may contribute to PCD, and that cilia are not always immotile.\textsuperscript{351} When compared to normal (Fig. 5.40A), the most commonly observed ultrastructural defects are the complete absence of dynein arms or the selective absence of either inner or outer arms (Fig. 5.40B). Other derangements of the axoneme contributing to PCD include defective or absent radial spokes (Fig. 5.41D), transposition of microtubules (Fig. 5.41C) (well seen in longitudinal sections of cilia), central microtubular agenesis, absence of nexin links, agenesis of cilia, or rarely, bizarre cystic dilatation of ciliary shafts.\textsuperscript{352-356} Nonspecific findings such as ciliary blebs, megacilia, compound cilia, and displaced microtubules may accompany the more specific defects, but are also frequently present in inflammatory airway disease of diverse causes including infectious bronchitis, CF, or air pollution.\textsuperscript{356-361} Some patients with structurally normal cilia and a normal ciliary beat frequency may develop the clinical manifestations of PCD due to ciliary disorientation, resulting in uncoordinated ciliary motion (Fig. 5.40E).\textsuperscript{362,363} Ciliary disorientation has also been described in individuals with infectious bronchitis (including CF), but the degree of disorientation is usually not as great as in those in whom the defect is primary, and the disorientation secondary to infection typically resolves after effective antibiotic treatment.\textsuperscript{299}

The diagnosis of PCD is established by ultrastructural analysis of respiratory epithelium in conjunction with typical clinical manifestations, exclusion of other causes of chronic airway inflammation, and documentation of abnormal ciliary motion by phase contrast microscopy.\textsuperscript{344,364,365} Mucosal samples obtained by endoscopic

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{5.40.png}
\caption{Kartagener’s syndrome. A. Dextrocardia (situs inversus). B. Bronchogram showing cylindrical bronchiectasis.}
\end{figure}
Figure 5.41. Primary ciliary dyskinesia (PCD). A. Normal ciliary cross section. Note the 9 + 2 microtubular arrangement, radial spokes, and inner and outer dynein arms. B. PCD. Complete absence of dynein arms. C. PCD. Transposition. A peripheral doublet has migrated centrally, giving an 8 + 2 pattern. D. PCD. Radial spoke defect. Migration of peripheral doublet internally, with displaced central tubules. Radial spokes are in disarray. E. Ciliary disorientation (left lower panel). Central axes are randomly oriented compared to parallel axes in normal (right lower panel). (B–D: courtesy of James McMahon, Ph.D., Cleveland Clinic Foundation. E: from de Jongh and Rutland, with permission from the American Thoracic Society.)
biopsy or brushing are examined by transmission electron microscopy. In patients with PCD, nasal mucosal samples are reflective of bronchial changes when most cilia are abnormal. When only few cilia are structurally abnormal in a patient in whom the diagnosis of PCD is highly suspected, a bronchial sample is required. Abnormalities in sperm flagella may differ in type and quantity from those of respiratory cilia within the same patient, suggesting separate genetic control of axonemal structures at differing loci.

The lung pathology in PCD is postinfective in appearance. Both saccular and cylindrical bronchiectasis may be present with the predominant histologic pattern of follicular bronchiectasis. Neither bronchial mucus stasis nor squamous metaplasia is prominent. Chronic interstitial pneumonitis, peribronchial fibrosis, and atelectasis accompany the bronchiectatic changes.

Studies to date suggest that PCD is a genetically heterogeneous disorder. The molecular basis of PCD has been localized in a few instances to mutations in the human dynein axonemal heavy chain (DNAH5) located on chromosome 5, or in the intermediate dynein chain gene 1 (DNAI1) on chromosome 9. A mutation in the dynein axonemal heavy chain type 11 (DNAH11) has been associated with PCD and situs inversus, without evident ultrastructural ciliary changes. Ongoing studies on genetically engineered knockout mice may uncover other genetic defects associated with PCD.

Young’s Syndrome

In 1970 Donald Young, a urologist, reported a series of patients with obstructive azoospermia, 54% of whom had associated respiratory conditions including bronchitis and bronchiectasis. This condition was initially designated as Berry-Perkins-Young syndrome and later shortened to Young’s syndrome. Several other studies have subsequently been published confirming Young’s original observations. In Handelsman et al.’s series of 19 patients, nearly all had chronic cough, sputum production, and recurrent pulmonary infections. Bronchiectasis and chronic sinusitis were each present in about two thirds of patients. In one study it was estimated that Young’s syndrome accounted for approximately 3% of all patients who presented with bronchiectasis of unknown etiology (equivalent to the prevalence of CF and slightly greater than that of PCD).

Azoospermia in Young’s syndrome is the result of retention of semen in an enlarged epididymal head. Motility studies have demonstrated impaired upper airway mucociliary transport; however, ciliary beat frequency and ultrastructure are normal. In patients with Young’s syndrome, sweat chloride concentration and the electrical potential difference across the nasal epithelium are normal. The respiratory symptoms in Young’s syndrome have been suggested to be the result of altered viscoelastic properties of airway secretions, but the basic molecular defect is unknown. An association with mercury toxicity has been hypothesized. Friedman and colleagues evaluated mutations of CFTR in a cohort of patients with Young’s syndrome and found that the prevalence of mutations did not differ significantly from the expected carrier frequency in the general population.

Pulmonary involvement is generally less severe than in CF. Bronchiectasis tends to occur at an early age and predominantly involves the lower lobes. Pulmonary function tests indicate mild obstruction with decreased FEV1 and increased residual volume. Although a number of patients have undergone lung resections for bronchiectasis, the pathologic features of bronchiectasis in Young’s syndrome have not been well described, and it is uncertain if there are any distinctive histopathologic changes. From a diagnostic standpoint it is important to exclude CF and PCD, each of which may be clinically misclassified as Young’s syndrome. The distinguishing characteristics among these three conditions are presented in Table 5.4.

| Table 5.4. Comparative features of congenital disorders of bronchiectasis and obstructive azoospermia |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Cause of Infertility** | CF (CBAVD) | PCD (Immotile sperm) | Young’s syndrome (Retained semen in epididymis) |
| Sweat chloride | Increased | Normal | Normal |
| Nasal transepithelial electrical potential | Increased | Normal | Normal |
| Pancreatic insufficiency | Present | Absent | Absent |
| Mucociliary clearance | Reduced | Reduced | Reduced |
| Severity of lung disease | Severe | Moderate | Mild |
| Localization of bronchiectasis | Generalized, UL dominant | Unspecified | LL |
| CFTR mutations | Present | Absent | Absent |
| Ciliary ultrastructure | Normal | Abnormal | Normal |
| Situs inversus | Absent | Present (50%) | Absent |

CBAVD, congenital bilateral absence of vas deferens; UL, upper lobe; LL, lower lobe; CF, cystic fibrosis; PCD, primary ciliary dyskinesia.
α₁-Antitrypsin Deficiency

Bronchiectasis has been reported in individuals with α₁-antitrypsin (AAT) deficiency, but its prevalence has been variable, with some series suggesting frequent occurrence and others not (see also Chapter 24). Orell and Mazodier, using whole lung macrosections, identified cylindrical bronchiectasis in three of six patients with AAT. King et al. identified six of 14 patients with AAT deficiency to have CT evidence of bronchiectasis. Cystic bronchiectasis was seen in two patients and cylindrical bronchiectasis in four. Histologic evaluation of two patients revealed emphysema and dilatation of large and small airways with multifocal disruption of bronchiolar elastic fibers. In a review of the pulmonary pathology of 42 patients enrolled in the national registry for individuals with severe deficiency of AAT, mild or moderate bronchiectasis was identified pathologically in only six patients (14%) (Fig. 5.42B). In the entire clinical registry, bronchiectasis was self-reported in a small minority of patients (3.4%). A more frequent histologic finding seen in 46% of autopsied patients in the registry was ectasia of membranous bronchioles in areas of severe emphysema (Fig. 5.42B). These observations suggest that bronchiectasis in AAT is secondary to matrix destruction in small airways coupled with loss of airway support due to severe emphysema (see also Chapter 24). Some patients with AAT and bronchiectasis have other associated causes of bronchiectasis such as CF, immune deficiency, or childhood pneumonia.

Eighteen percent to 27% of patients with severe, AAT-replete emphysema have localized bronchiectasis as a minor contributory factor to airflow obstruction. Thurbeck cautioned that so-called cylindrical bronchiectasis in patients with severe emphysema in the general population may simply represent airway dilatation in full inspiration. Conversely, in patients in whom bronchiectasis is the primary cause of airflow obstruction, emphysema in the immediate vicinity of the ectatic airways is frequently observed. Anderson and Foraker documented alternating ectasia and narrowing of small airways as a constant feature in severely emphysematous lungs.

Williams-Campbell Syndrome (Congenital Bronchiectasis)

Williams-Campbell syndrome is a rare disorder in which extensive loss of bronchial cartilage is associated with diffuse cystic bronchiectasis without other recognized predisposing factors. The clinical presentation that commences in infancy may include cough, dyspnea on exertion, cyanosis, and clubbing. On chest radiograph large thin-walled cysts reside in hyperinflated lungs. High-resolution CT scan characteristically shows central, cystic, thin-walled airways that collapse upon expiration. The clinical course is one of recurrent pulmonary infections leading to respiratory failure. Patients may survive into adulthood and require lung transplantation. As described in the original report by Williams and Campbell and substantiated in subsequent morphologic studies, the lungs grossly exhibit extreme saccular and cystic bronchiectasis. Microscopically, dilated airways have very thin walls with minimal inflammation. Cartilage is absent or markedly deficient from the fourth to the eighth divisions of subsegmental bronchi. First- and second-order bronchi usually have a normal cartilage investment. Panacinar emphysema or emphysema localized to the peribronchial zone is usually also present. Bronchiolitis obliterans has also been reported.

Figure 5.42. α₁-Antitrypsin deficiency. A. Saccular bronchiectasis involving middle lobe. B. Ectasia of membranous bronchiole. There is adjacent panacinar emphysema.
FIGURE 5.43. Williams-Campbell syndrome. A. Note severe central cystic bronchiectasis. B. Markedly dilated, thin-walled airways devoid of cartilage. There is minimal chronic inflammation. (Courtesy of Dr. Tim Oury, Duke University Medical Center.)

The Williams-Campbell syndrome has been considered to be the result of a congenital absence of cartilage in the subsegmental airways. Morphologic studies documenting absent cartilage and insignificant inflammation, and rare reports of familial occurrence have been used to support this view. However, given the propensity for cartilage loss in acquired saccular bronchiectasis of diverse etiologies, the Williams-Campbell syndrome remains a controversial entity, and its congenital origins have yet to be proven beyond question. The Williams-Campbell syndrome has not been associated, nor is it to be confused, with congenital lobar emphysema, in which cartilage is focally deficient, usually in upper lobe bronchi, leading to bronchial collapse and air trapping (see also Chapter 6).

Tracheobronchomegaly

Tracheobronchomegaly (TBM) is a condition of marked dilatation of the trachea and major bronchi, often associated with recurrent respiratory infections. TBM can be congenital, or at least evident in early life, in which it is termed Mounier-Kuhn syndrome (see Chapter 6). It has occurred in several cases of Ehlers-Danlos syndrome, suggesting it may be related to poor elastic support, or perhaps to loss of other matrix components as in chondromalacia. Tracheobronchomegaly occurs in adults, mostly in men in their fourth and fifth decades, and can be an acquired condition secondary to sustained inflammation affecting the trachea, such as in chronic bronchitis secondary to tobacco abuse, cystic fibrosis, trauma, emphysema, or pulmonary fibrosis.

A comprehensive review and an intriguing study of various pulmonary fibrotic reactions associated with this entity was reported by Woodring et al. These investigators evaluated the tracheal diameter on plain chest radiography in a series of 34 cases of fibrotic lung reactions, and found enlargement of the trachea in 10 (29%). The associated lung diseases were idiopathic pulmonary fibrosis and sarcoidosis in four patients each, and progressive histoplasmosis in two patients. In seven of these patients as well as in nine of 24 patients (38%) who did not meet initial radiographic criteria for tracheal dilatation, tracheomegaly developed or progressed over time. Tracheobronchomegaly was usually associated with moderate-to-severe restrictive pulmonary defects, and it was proposed that shrinkage of the lung tissue retracts all adjacent spaces including the trachea in a manner similar to traction bronchiectasis.

Regardless of the cause of TBM, airway dilatation may extend distally. Bronchomegaly simulates bronchiectasis, probably impairs lung clearance, and promotes recurrent bronchopulmonary infection, which paradoxically may induce secondary bronchiectasis. Roditi and Weir identified tracheobronchomegaly in 17% of patients with evidence of bronchiectasis on CT scan, thereby emphasizing the frequent association and possible causal connections between these two conditions.

Tracheobronchomegaly is predominantly a radiologic diagnosis, and its pathologic features have not been
well characterized. Associated radiographic features include marked tracheal wall thinning, scalloping due to mural inrolling, bronchial diverticula, and collapse on expiration.415,416 The diagnostic criteria of TBM by CT scan are a tracheal diameter of greater than 3 cm (measured 2 cm above the aortic arch) and diameters of 2.4 and 2.3 cm for the right and left main bronchi, respectively.415,417 Tracheobronchomegaly must be distinguished from saber-sheath trachea, seen in some patients with and 2.3 cm for the right and left main bronchi, respectively.415,417 Tracheobronchomegaly must be distinguished from saber-sheath trachea, seen in some patients with emphysema, in which there is a decrease in tracheal coronal diameter and increased sagittal diameter415,418

**Immunodeficiency States**

Patients with immune deficiency, especially hypogammaglobulinemia due to X-linked agammaglobulinemia or common variable immunodeficiency (CVID), are predisposed to develop bronchiectasis secondary to recurrent pulmonary infections.419-422 Chronic pulmonary disease is the most common long-term complication in patients with hypogammaglobulinemia.422 Common variable immunodeficiency, a heterogeneous immunodeficiency syndrome characterized by depressed levels of serum immunoglobulin G (IgG) and defective antibody response to antigen challenge, is associated with sinusitis, recurrent pneumonia, and chronic sputum production in up to 90% of patients.423 Patients with CVID also have an increased incidence of autoimmune diseases, and as with other primary immunodeficiency syndromes, a tendency toward lymphoproliferative disorders (see Chapter 32).422,424 In this population there is a spectrum of lung abnormalities including interstitial fibrosis (>80% of patients), pneumonia, lymphoid interstitial pneumonia (LIP), sarcoidosis-like granulomatous disease (10%), lung abscess, and bronchiectasis.422,425

Bronchiectasis is the most common radiologic finding and may be identified in over 30% of patients by chest x-ray, and in up to 80% of patients by HRCT.424,426 By HRCT bronchiectasis may be either focal or multilobar, and is of the cylindrical or rarely cystic type.420,426 The lower and middle lobes tend to be predominantly involved.420,424 Although mucociliary clearance is impaired in these patients, ciliary ultrastructure is normal.427 There is little information on the histopathology of bronchiectasis in CVID.428,429 Hill and colleagues429 noted severe bronchiectasis, emphysema, fibrosis, and granulomas in the lung explant of a 37-year-old man with CVID. No unique features of bronchiectasis were described. Patients with CVID are treated with immunoglobulin replacement therapy, which reduces the severity and frequency of respiratory infections.

Symptomatic bronchiectasis, identified by HRCT scan, has also been reported in patients with HIV disease in whom it is associated with rapidly progressive airways obstruction.430,431 King and colleagues432 correlated airway dilatation on CT scan with increased neutrophils on bronchoalveolar lavage. A single report of a transbronchial biopsy showed only nonspecific lymphocytic peri-bronchiolitis.431 The pathogenesis of bronchiectasis in HIV patients is likely consequent to bronchial damage from recurrent pneumonia and bacterial bronchitis in this immunosuppressed population.430,433 Frequently cultured microorganisms include *H. influenzae*, *P. aeruginosa*, and *S. pneumoniae*.430,433

Bronchiectasis also occurs as a complication of lung transplant–associated immunosuppression and bronchiolitis obliterans and is further discussed in Chapter 23.434,435

**Rheumatoid Arthritis**

Symptomatic bronchiectasis is estimated to occur in 1% to 3% of patients with rheumatoid arthritis (RA), although with HRCT scan, up to 30% of patients with RA can be shown to have cylindrical bronchiectasis.435,436,437 Early autopsy studies of patients with RA provided a prevalence of bronchiectasis of 0% to 12%.436-441 In some studies bronchiectasis typically preceded the development of arthritis, leading to the interesting hypothesis that chronic suppurative airway disease is involved in the pathogenesis of RA.442-444 Shadick and colleagues,444 however, reported 23 patients with bronchiectasis and RA, of whom 18 developed bronchiectasis as a late complication of severe RA. Bronchiectasis may also be more frequent in patients with RA-associated Sjögren’s syndrome.442,445 Bronchiectasis associated with RA cannot be adequately ascribed to either traction bronchiectasis or therapeutic immunosuppression.436,444

The morphologic features of RA-associated bronchiectasis are not well documented. By CT scan, cylindrical bronchiectasis primarily involves the middle and lower lung zones.437,444,445 Baggenstoss and Rosenberg438 based on their 1943 autopsy series, noted, “The lesions of this condition [bronchiectasis] ... were in no way distinctive.” Other pulmonary manifestations of RA are covered in Chapter 20.

**Inflammatory Bowel Disease**

Bronchiectasis is part of the spectrum of lung involvement in patients with inflammatory bowel disease (IBD), ulcerative colitis more so than Crohn’s disease (see also Chapter 20).446,447 Suppurative bronchiectasis may also develop after proctocolectomy for either of these conditions.447,448

In the 1993 literature review of Camus et al.,446 bronchiectasis was identified in six patients with ulcerative colitis out of 33 patients (18%) with IBD-associated lung disease.
FIGURE 5.44. Ulcerative colitis. A. Bronchiectasis, with lumen exudate (left upper), dense mural chronic inflammation, and enlarged bronchial artery. B. Dense submucosal chronic inflammation, mainly lymphocytic. Germinal centers are inconspicuous. (Courtesy of Dr. Thomas V. Colby, Mayo Clinic, Scottsdale.)

(27 with ulcerative colitis, six with Crohn’s disease). Bronchiectasis tended to involve the posterior lower lobes. Histologically a dense cuff of lymphocytes typically occupies the submucosa, and squamous metaplasia replaces the overlying epithelium (Fig. 5.44). The chronic inflammatory infiltrate involves bronchial glands and ducts; however, lymphoid germinal centers are usually absent, distinguishing ulcerative colitis-associated bronchiectasis from the usual pattern of follicular bronchiectasis (Fig. 5.44B). Neutrophils infiltrating the mucosa and spilling into the dilated bronchial lumen impart a suppurative appearance in some cases. Direct immunofluorescence staining of bronchial biopsies in three patients with ulcerative colitis showed deposits of immunoglobulin and complement in bronchial structures. Other cases of diffuse bronchiectasis in heroin users appear to be unrelated to aspiration. See Chapter 31 for other pathologic features of heroin toxicity.

In adults, severe direct chemical injury such as ammonia gas inhalation or aspiration can cause bronchiectasis. Delayed-onset bronchiectasis has also been described starting 12 years after smoke inhalation.

Acknowledgments. The authors are deeply appreciative to Diane Gillihan for expert secretarial assistance, Vince Messina for photography, and the staff of the Brittingham Memorial Library for bibliographic support.

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Chemical Injury

Bronchiectasis is reported as a late sequela of heroin-associated pulmonary edema. The bronchographic features include diffuse or localized cylindrical and varicose bronchiectasis. Aspiration pneumonia and bronchiolitis are etiologic factors in some patients, and bronchial ulceration and foreign-body giant cells have been observed at autopsy. Other cases of diffuse bronchiectasis in heroin users appear to be unrelated to aspiration. See Chapter 31 for other pathologic features of heroin toxicity.
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