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Emphysema and Chronic Bronchitis

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The diagnosis of chronic obstructive pulmonary disease (COPD) is predicated upon the recognition of its two major forms: emphysema and chronic bronchitis. These distinct entities represent different manifestations of COPD, although they frequently coexist in the same individual. Physiologic impairment occurs as a consequence of the impediment of airflow and air trapping as measured by pulmonary function testing. Other forms of airflow obstruction are discussed in the chapters on bronchial obstruction (Chapter 5), asthma (Chapter 15), and pathology of small airways (Chapter 25).

Chronic obstructive pulmonary disease is a major cause of morbidity and mortality throughout the world. It has been estimated that 5% to 15% of adults in industrialized nations suffer from COPD,[1] and COPD is the fourth leading cause of death in the United States, exceeded only by cardiovascular diseases, cancer, and cerebrovascular diseases. By 2020, COPD may become the third leading cause of death worldwide, commensurate with the rising rates in lung cancer.[2] Chronic obstructive pulmonary disease is almost entirely preventable. The major cause by far is cigarette smoking, but air pollution (including passive smoking) and occupational exposures are also contributing factors.[3–6]

The early recognition of these disorders is important, not only in terms of prevention of further progression, but because advances in treatment developed over the past two decades can reduce the incidence of exacerbations of COPD. The mainstay of treatment is long-term bronchodilators and inhaled corticosteroids.[7]

Emphysema is a morphologic condition best observed in lung specimens that have been fixed, either by inflation fixation followed by freeze-drying or by intrabronchial instillation of formalin under pressure. When this methodology is employed, the prevalence of emphysema is much greater than the clinical prevalence of COPD would imply. Approximately 50% of smokers have detectable emphysema in inflation-fixed lungs, with an average extent of 25% of surface area as determined by point counting.[8] Emphysema is also detected in approximately 16% of nonsmokers, with a mean extent of only 7%. Regression analysis of the extent of emphysema and age of death indicates that emphysema begins at about the age of 18 years, which coincides with the average age of initiating cigarette smoking (Fig. 24.1).[9]

Chronic bronchitis, in contrast with emphysema, has a clinical definition (see below). The morphologic correlate of this clinical syndrome is mucous gland hyperplasia and an increase in the proportion of goblet cells in the surface mucosa. The pathologic findings, clinical correlates, etiology, and pathogenesis of chronic bronchitis and emphysema are discussed in more detail in the following sections.

Chronic Bronchitis

Definition

Chronic bronchitis is defined clinically as a productive cough for at least 3 months out of the year for 2 consecutive years, with no other apparent explanation. This clinical definition excludes patients with cystic fibrosis and other causes of bronchiectasis, which show similar histologic features in the large airways (see Chapter 5).

Pathology

Gross examination of bronchi in patients with chronic bronchitis may show mucous plugging and prominence of bronchial mucosal pits. The latter represent the orifices of bronchial mucous glands, which are dilated from mucous distention. In addition, cross-sectional views may show thickening of the bronchial walls with narrowing of the lumen (Fig. 24.2).

The histologic correlate of chronic bronchitis is the presence of mucous gland hyperplasia. This manifests as an increased percentage of the bronchial wall occupied by

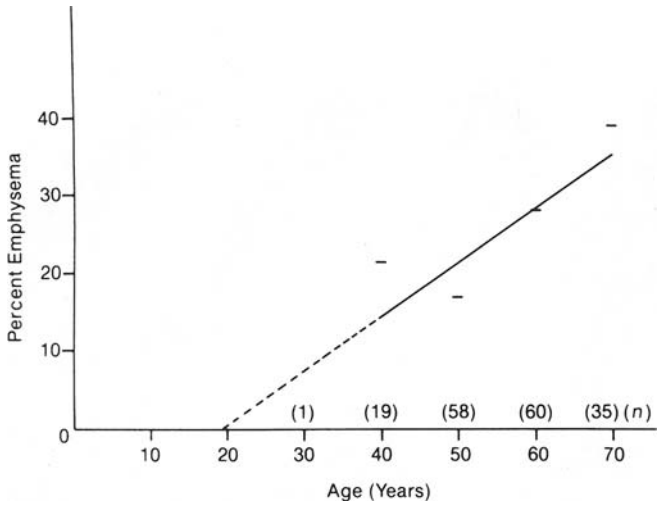


FIGURE 24.1. Regression of correlation between age at death and percentage of lung involvement by centrilobular emphysema, determined by point counting, in 173 autopsies of smokers who had the disease. Slope represents disease progression at rate of 7% per 10 years. Correlation coefficient is 0.27, and probability *(p)* that this trend might have occurred by chance is <.001. The equation for the regression line is as follows: Emphysema extent = 0.69 × Age – 13.2. Values in parentheses represent number of cases seen in each 10-year age group. Horizontal bars represent average extent of emphysema per group.

submucosal mucous glands (Fig. 24.3). Classically, this increase has been defined by the Reid index, which is the ratio of the width of the mucous glands to the distance between the basal lamina of the mucosa and the inner

FIGURE 24.2. Bronchial cross sections demonstrate severe mural thickening and luminal narrowing. Lung parenchyma shows mild emphysema. Barium sulfate impregnation. (From Tomashefski JF Jr. Pathology of advanced obstructive lung disease: emphysema, chronic bronchitis, bronchiolitis obliterans, and bronchiectasis. In: Maurer JR, ed. Non-neoplastic advanced lung disease. New York: Marcel Dekker; 2003:1–27, with permission.)

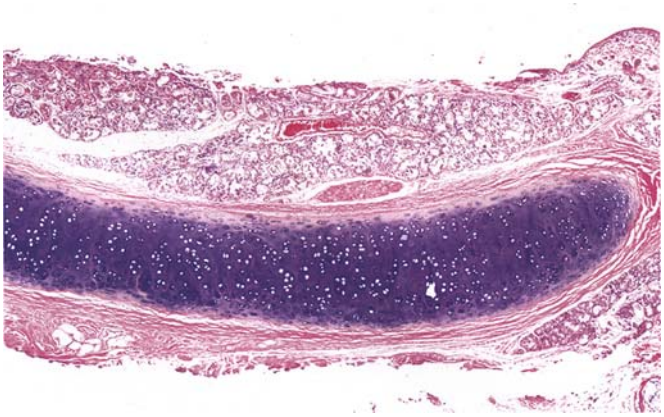


FIGURE 24.3. Low-power view of bronchus showing bronchial mucous gland hyperplasia. The ratio of the thickness of the mucous gland layer to the distance from the top of the cartilage to the respiratory epithelium basement membrane (Reid index) is approximately 0.8. Normal value is 0.4 or less.

perichondrium (see Fig. 2.7B in Chapter 2).[10] Since this width may vary from site to site in the bronchial wall, an average value is obtained from the measurement at several locations. The index is normally less than 0.4. Values of 0.5 or greater are indicative of mucous gland hyperplasia. There is a direct correlation between the value of the Reid index and the volume of daily sputum production by the patient.[10] In some cases, oxyphil metaplasia of the mucous glands may be observed. In the authors' experience, this is usually seen in the bronchial resection margin of cigarette smokers who have undergone resection for lung cancer (see Fig. 2.8B in Chapter 2).

Other findings in chronic bronchitis include an increase in proportion of goblet cells in the surface mucosa (Fig. 24.4) and distention of mucous gland ducts (Figs. 24.5 and 24.6). Surface mucosal goblet cells normally average about one per 20 ciliated cells in the trachea and are progressively fewer in lobar and segmental bronchi. In chronic bronchitis, goblet cells may actually outnumber the ciliated cells. In some cases, squamous metaplasia or diffuse reserve cell hyperplasia may also be observed. A chronic inflammatory infiltrate composed of lymphocytes and plasma cells is a variable feature and may be entirely absent. For this reason, it has been suggested that the term *chronic large airways disease* is preferable to *chronic bronchitis,* which implies an inflammatory component.[8]

The morphology of chronic bronchitis is similar whether it is due to cigarette smoking, air pollution, or occupational exposures. In patients with chronic bronchitis secondary to silica exposure, fibrosis may be observed in the wall of the large airways (Fig. 24.7). In some cases, this may result in obstructive abnormalities.[11]

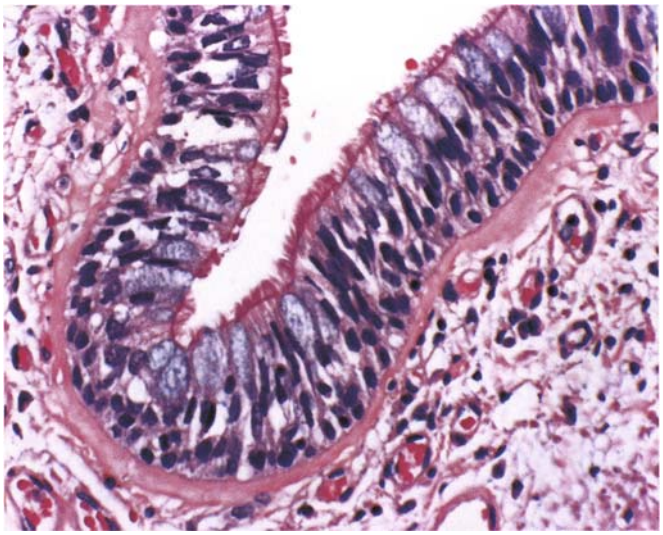


FIGURE 24.4. High-power view of bronchial mucosa showing goblet cell hyperplasia. Under normal conditions, goblet cells represent one out of every 20 respiratory epithelial cells or less.

Clinical Correlation

By definition, chronic bronchitis manifests as a productive cough. Studies have shown that the absolute gland area of bronchial mucous glands is significantly related to the volume of sputum produced by the individual patient.[12] Similarly, the volume proportion of mucous glands (ratio of the area of individual glands to the area of the bronchial wall) also correlates significantly to sputum volume. Interestingly, in this study, the Reid index as defined above did not show a significant correlation with sputum volume.[12]

A common misconception is that chronic bronchitis is associated with obstructive changes on pulmonary function tests. However, none of the measures of mucous gland volume correlate significantly with the forced expiratory volume in 1 second (FEV_1), the most common measure of obstruction. Furthermore, the volume of sputum production also does not correlate with the FEV_1.[12] Confusion occurs because patients with chronic bronchitis often (but not invariably) also have small airways disease (see Chapter 25) or emphysema. These

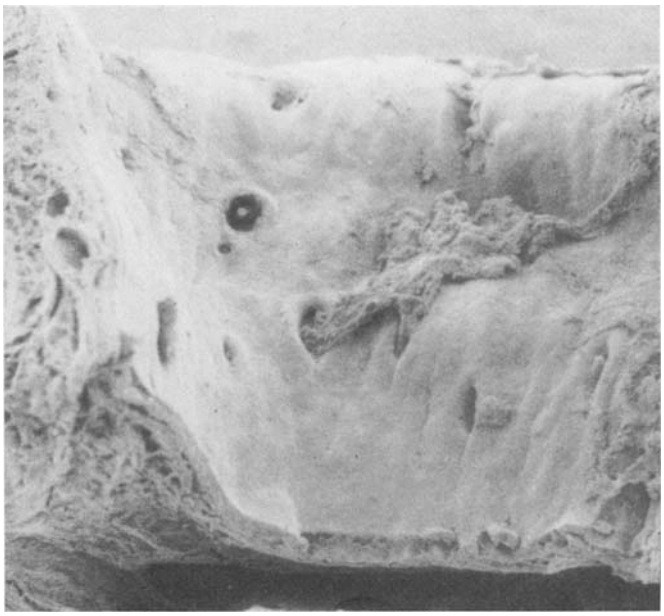


FIGURE 24.6. Secondary electron image of bronchial surface shows dilated pores with mucous streaming onto the surface from one of the pores. Scanning electron microscopy, ×21. (From Simel DL, Mastin JP, Pratt PC, Wisseman CL, Shelburne JD, Spock A. Scanning electron microscopic study of the airways in normal children and in patients with cystic fibrosis and other lung diseases. Pediatr Pathol 1984;2:47–64, with permission.)

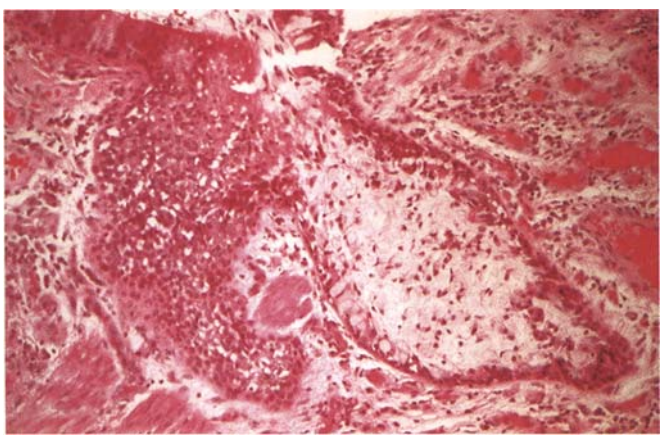


FIGURE 24.5. This bronchial gland duct is distended with mucus.

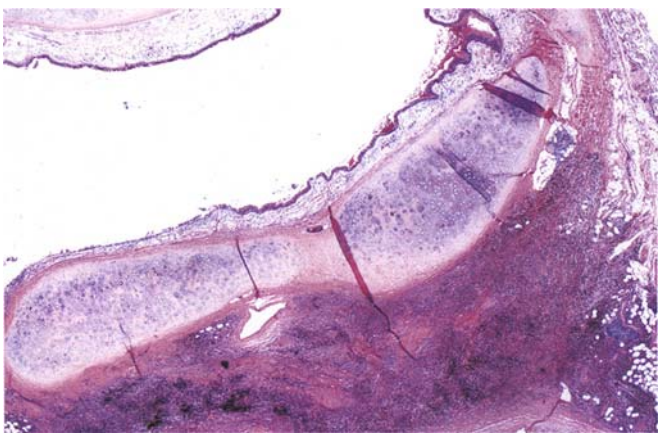


FIGURE 24.7. Low-power view of bronchus showing dense dust deposits and fibrosis in the bronchial wall exterior to the bronchial cartilage. The patient was a coal miner.

TABLE 24.1. Etiologic factors in chronic bronchitis

Cigarette smoke
Marijuana smoke
Occupational dust exposure (industrial bronchitis)
Air pollution (including passive smoking)

latter conditions cause airway obstruction, and sputum production in chronic bronchitis is a separate factor from other causes of obstructive lung disease.[13,14]

Etiology and Pathogenesis

Etiologic factors for chronic bronchitis are summarized in Table 24.1. By far the most important factor is cigarette smoking, and there is a dose-response relationship.[15,16] Qualitatively similar abnormalities may be seen in habitual, heavy smokers of marijuana.[17] Occupational exposure to dust (e.g., coal miners or textile workers) can also cause excess sputum production, a condition that has been referred to as *industrial bronchitis*.[18,19] Finally, air pollution has been implicated in the etiology of chronic bronchitis.[4]

The conditions listed in Table 24.1 share in common exposure of the tracheobronchial epithelium to large numbers of inhaled particulates. For example, cigarette smoke contains 3×10^9 to 3×10^{10} particles per milliliter, with mean particulate diameter of 0.2 to 0.4 μm.[20,21] The irritative effects of these particulates deposited on the airway mucosa are believed to cause epithelial injury, which in turn leads to metaplastic changes in the mucosal epithelium and hyperplasia of bronchial mucous glands. The mechanism likely involves oxidant stress with subsequent activation of nuclear factor (NF)-κB and increased expression of interleukin-8 messenger RNA.[22–24] This in turn causes infiltration by inflammatory cells, including neutrophils, macrophages, and lymphocytes. The latter primarily include CD8-positive lymphocytes.[25] There is a concomitant increase in epithelial permeability.[22] Endotoxin may also play a role in airway disease caused by exposure to cotton dust (byssinosis).[26]

Emphysema

Definition

Emphysema is defined as a group of pulmonary diseases characterized by abnormal enlargement of the air spaces distal to terminal bronchioles with destruction of alveolar walls. It is morphologically distinct from hyperinflation, in which the alveolar spaces are distended without evidence of destruction. An example is congenital lobar hyperinflation, a condition caused by abnormal bronchial development resulting in air trapping within a lobe. Although this condition has been referred to as congenital lobar emphysema, there is no true destruction of alveoli (see Fig. 6.20 in Chapter 6).

Classification

A number of classifications have been proposed for emphysema.[27] The classification used by the authors is shown in Table 24.2.[8,28] This classification has both morphologic and clinical utility. Morphologically, the various forms are readily distinguishable, especially when inflation-fixed specimens are employed. Clinically, the diffuse forms of emphysema are characterized by lung destruction that can result in pulmonary impairment. Localized forms do not cause impairment, but can be important as a cause of spontaneous pneumothorax.

Centrilobular (Proximal Acinar) Emphysema

The secondary lobule constitutes a group of air spaces partially surrounded by a fibrous (secondary lobular) septum.[29] In the human lung, fibrous septa are highly variable in their prominence from individual to individual and even within the same lung. The pulmonary acinus is that portion of lung supplied by one terminal bronchiole. There is some variation in the number of acini per secondary lobule, averaging from three to eight and ranging up to about 20.[8] Thus the acinus is a subset of the secondary lobule (see Chapter 2).

Centrilobular emphysema (CLE) is the most common form of emphysema, accounting for about 85% of cases. This disorder tends to begin in the central part of the lobule or acinus, and, as the disease progresses, may involve the entire acinus or lobule. The key to the recognition of CLE is the identification of adjacent foci of normal alveolar architecture and enlarged air spaces with alveolar wall destruction (Fig. 24.8). Even though progression to more severe involvement may result in destruction of entire lobules, CLE can still be accurately diagnosed simply by observing less involved areas, where normal lung adjacent to emphysematous destruction will always be found. Centrilobular emphysema does not progress to involvement of all lobules, since respiratory failure typically supervenes when 60% or more of the lung is involved, and the greatest extent of involvement observed in a series of 192 cases was 90%.[8]

TABLE 24.2. Classification of emphysema

Pratt classification[8]	Thurlbeck classification[28]
Centrilobular emphysema	Proximal acinar emphysema
Panlobular emphysema	Panacinar emphysema
Localized emphysema	Distal acinar emphysema
Paracicatricial emphysema	Irregular emphysema

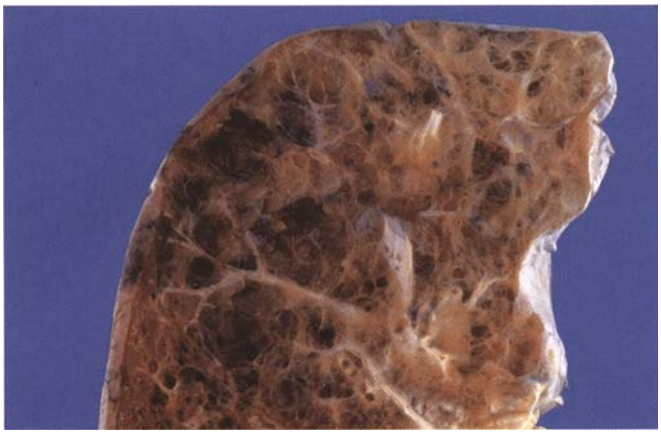


FIGURE 24.8. Inflation-fixed lung specimen with moderately severe centrilobular emphysema, showing numerous foci of emphysematous destruction adjacent to macroscopically normal lung parenchyma. Most areas of emphysema in this specimen are associated with pigment deposition.

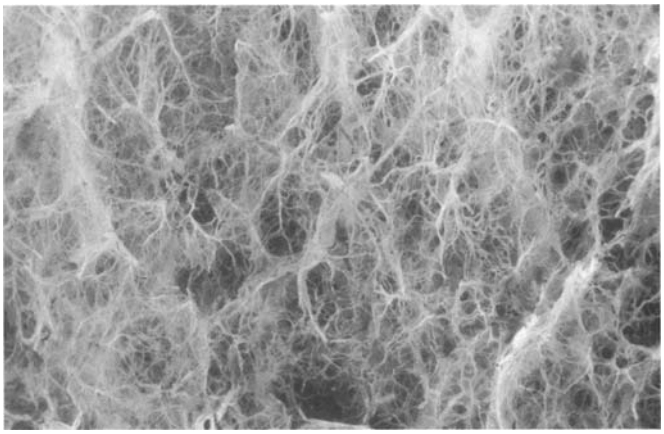


FIGURE 24.9. Macroscopic close-up view of inflation fixed lung specimen in patient with panlobular emphysema. There is uniform destruction of lung parenchyma.

Centrilobular emphysema is typically more severe in the upper lobes, and as the disease progresses, more areas of lung show emphysematous destruction. Grading of severity is based on the proportion of the cut surface of an inflation-fixed specimen that shows emphysematous destruction. Trace CLE involves no more than 2% of the cut surface of a central slice of the lung. Mild CLE involves 3% to 25%, moderate involves 26% to 50%, and severe more than 50% of the cut surface. Cases with destruction adjacent to secondary lobular septa of the pleura are invariably associated with other lesions in the centrilobular distribution. Therefore, these cases are included under the term *centrilobular emphysema.*[8]

Panlobular (Panacinar) Emphysema

Panlobular emphysema (PLE) accounts for approximately 5% of cases. The enlargement of air spaces with destruction of alveolar walls is evenly distributed from the center to the periphery of the lobule or acinus in PLE (Fig. 24.9). The destruction is also relatively uniform throughout the lung, although destruction tends to be more severe in the lower lobes (Fig. 24.10).

As defined herein, CLE and PLE are essentially mutually exclusive. The grading scheme as defined for CLE is not applicable to PLE, since point counting for the latter would result in a score of 100% (i.e., no normal alveolar architecture present). The more severe involvement of the lower lobes also helps distinguish PLE from CLE, which tends to be more severe in the upper lobes. The differing gross distribution of these two diseases is likely the result in differences in etiology and pathogenesis (see below).

Localized (Distal Acinar) Emphysema

Localized emphysema accounts for approximately 5% of cases of emphysema. The term *localized emphysema* refers to cases in which there is only one site (or at most a few sites) of severe emphysematous destruction of alveoli. The remaining pulmonary architecture is normal. The most common location is at the extreme apex of either or both lungs, but it may also occur in other locations (Fig. 24.11). Localized emphysema is a common cause of spontaneous pneumothorax in young adults.[30]

Localized emphysema can progress to sizable areas of pulmonary destruction. The word *bulla* is often used to describe such lesions when they exceed 1.0 cm in size. However, bullae may also occur in PLE or CLE

FIGURE 24.10. Lower portion of lung from patient with α_1–antitrypsin deficiency. There is marked involvement of the lower lobe with panlobular emphysema. Emphysematous destruction was also present but less severe in the upper lobe.

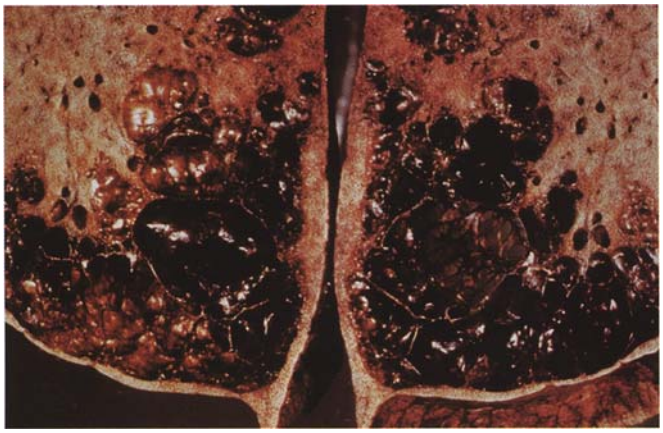


FIGURE 24.11. Localized emphysema in the lower lobe of an inflation fixed, freeze-dried lung specimen. No detectable emphysema was present in the remainder of the lung.

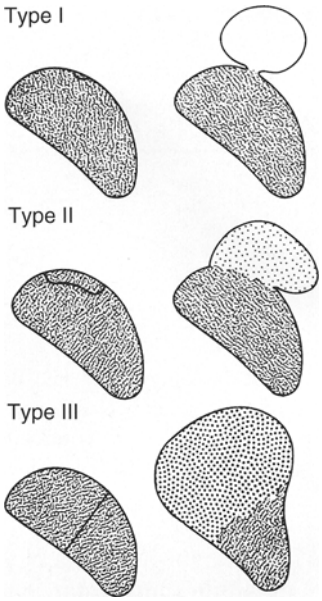


FIGURE 24.13. Diagramatic representation of types of bullae. I small amount of lung greatly overinflated giving narrow neck and empty sac; II relatively less overinflation of shallow layer of lung giving broad neck and usually at least lung remnants; III relatively less overinflation of large amount of lung, usually extending back to hilum giving no well defined neck and usually lung evenly through bulla. (Reprinted with permission from Ref. 31, Figure 114.)

(Fig. 24.12), so the term *bullous emphysema* is nonspecific and should be avoided as a synonym for localized emphysema. Reid[31] has classified bullae into three groups, based on the size of the lesions, the degree of lung destruction, and the protrusion of the bullae above the lung surface (Fig. 24.13). Type I involves a small amount of lung that is greatly overinflated, resulting in an empty sac with a narrow neck (Fig. 24.14). Type II consists of a shallow layer of lung with a broad neck and at least some lung remnants. Type III includes a large amount of lung parenchyma, often extending back to the hilum and with lung tissue remnants evenly distributed through the bulla (Figs. 24.12 and 24.13).

FIGURE 24.12. Lung specimen from a patient with centrilobular emphysema, illustrating giant bullous formation. The upper lobe is destroyed and replaced by a bulla (Reid type III, see Figure 24.13).

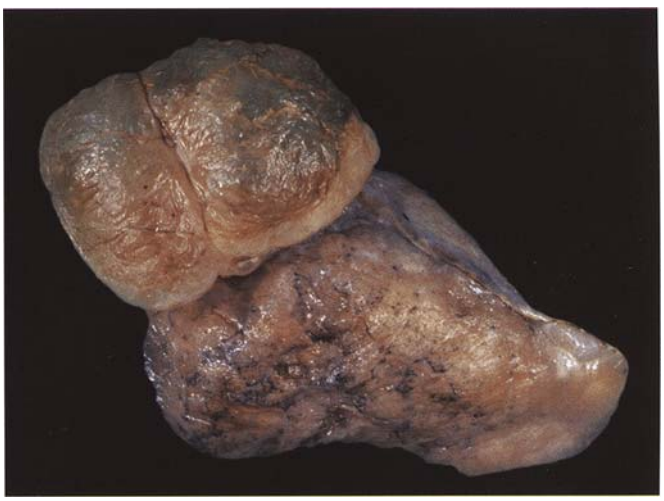


FIGURE 24.14. Type I bulla (upper) protrudes above the lung surface with a narrow neck and is devoid of lung remnants. (Courtesy of Dr. Joseph F. Tomashefski, Jr., MetroHealth Medical Center, Cleveland, OH.)

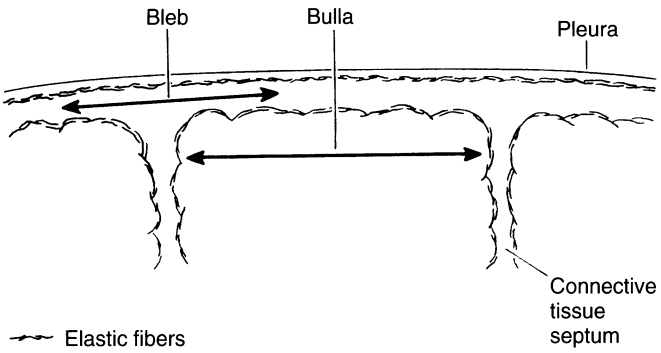


FIGURE 24.15. Diagram showing difference between bleb and bulla; being within pleura, a bleb is external to the internal elastic layer and not confined by connective tissue septa. (Reprinted with permission from Ref. 31, Figure 130.)

Bullae should be distinguished from blebs. Whereas the former are located within the substance of the lung, the latter are located within the visceral pleura (i.e., outside of the inner elastic lamina) (Fig. 24.15).[31] The terms *distal acinar* and *paraseptal emphysema* have also been used to describe some more diffuse forms of emphysematous destruction.[28] As noted above, these lesions are invariably accompanied by areas of typical CLE and are more properly classified as such.

Paracicatricial (Irregular) Emphysema

Paracicatricial emphysema refers to emphysematous destruction occurring adjacent to pulmonary scars. The scars may be consequent to old granulomatous inflammation (Fig. 24.16; see also Figs. 9.15 and 9.6C in Chapter 9), healed pulmonary infarcts, organized pneumonia, or pneumoconiosis. The emphysematous destruction occurs over a number of years, and the mechanism is poorly understood. In most cases, there are just a few foci of scarring, and the resultant emphysema has little physiologic significance. However, in some cases with extensive scarring (e.g., extensive healed disseminated tuberculosis), the distortion and volume changes may result in physiologic impairment similar to that seen in CLE.[32] Paracicatricial emphysema, also referred to as perifocal emphysema,[8] accounts for about 5% of cases.

In addition to paracicatricial emphysema associated with the scarring of pneumoconiosis, there is a mild form of emphysema associated with coal worker's pneumoconiosis. This form, sometimes called *focal emphysema*, manifests as areas of emphysematous destruction adjacent to interstitial deposits of coal dust.[33] This constellation of findings constitutes the coal dust macule (See Chapter 26). An example of "focal emphysema" in coal workers is CLE occurring in a cigarette-smoking miner. Nonsmoking coal workers rarely develop any type of emphysema with clinical impairment.[34]

Pathology

Gross Observations

The gross morphologic changes in emphysema are best observed on examination of inflation-fixed specimens. Emphysema begins as areas of destruction (holes in the lung) just visible to the naked eye. As the disease progresses, the lesions enlarge and become more numerous. Emphysematous foci are often associated with pigment deposition (Fig. 24.17), but pigmented areas are not invariably emphysematous.[35] Areas of emphysematous destruction are often traversed by fine strands, which represent the vasculature that once supplied the area of destruction. Emphysematous lesions that exceed 1.0 cm in maximum dimension are often referred to as *bullae*. Bullous lesions may become so large that they occupy a large proportion of the hemithorax. Such bullae are frequently traversed by the fine strands noted above (Fig. 24.18).

There is an increase in lung volume with progression of emphysema, and the volume of the lung correlates with the degree of emphysematous destruction (Fig. 24.19). Bullous lesions may protrude from the surface of the lung, resulting in a nodular appearance upon external examination. Bullae freely communicate with the underlying lung parenchyma, which can be demonstrated by

FIGURE 24.16. Inflation fixed lung specimen with paracicatricial emphysema due to old tuberculous scarring. Several caseous foci are present within the lung, and there is emphysematous destruction around these foci.

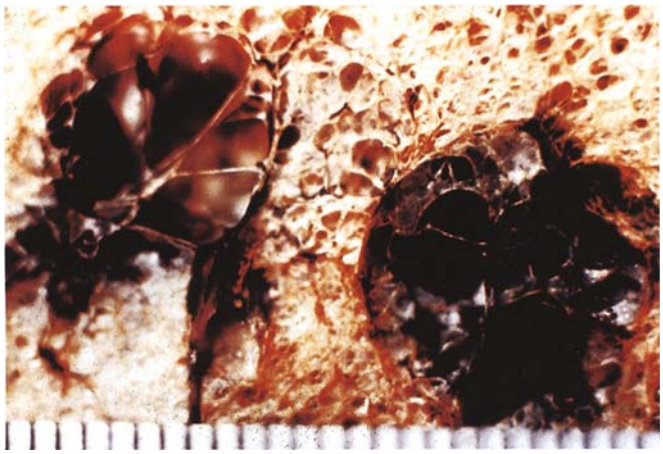


FIGURE 24.17. Close-up view of inflation-fixed, freeze-dried specimen of lung showing centrilobular emphysema, with foci of emphysematous destruction adjacent to areas of macroscopically normal lung parenchyma. The emphysematous foci are associated with pigment deposition in this specimen.

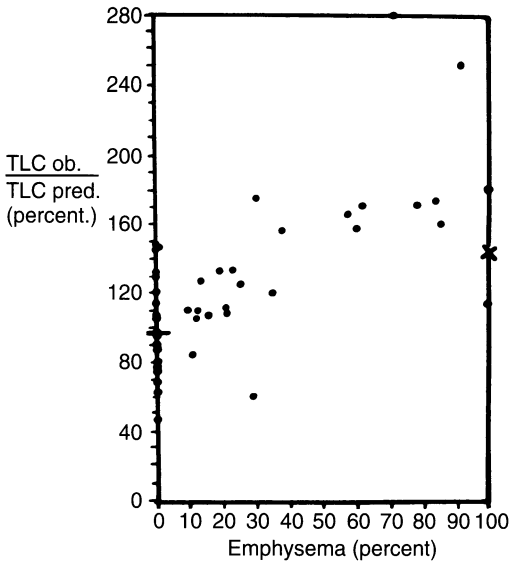


FIGURE 24.19. Graph showing the relationship between postmortem lung volume (y-axis) and percentage of lung involved with centrilobular emphysema as determined by point counting (x-axis). There is a trend for increasing lung volume with increased amounts of emphysematous destruction. TLC, total lung capacity; ob., observed; pred., predicted.

compressing the bulla in an inflation-fixed lung. Air is readily displaced into the surrounding lung parenchyma, and after release of the pressure, the bulla promptly reinflates to its original size. The bullous area is more compliant than the surrounding lung, and so it expands until the tension in its pleural surface equalizes the tension in the walls of adjacent intact alveoli.[8]

The basic lesion of emphysematous destruction can be observed by examining the cut surface of inflation-fixed specimens with the binocular dissecting microscope.[36–41] Holes or *fenestrations* in the walls of the alveolar septa are the earliest findings, and are readily seen at magnifications of 10× to 25×. Fenestrations are distinguished from the normal pores of Kohn by their larger and more variable size. Pores of Kohn are uniformly small and difficult to detect at these magnifications. As the fenestrations enlarge, the alveolar septum is reduced to a network of thin strands. These may in turn rupture, so that two alveoli then coalesce into a single space. This process may continue until bullous lesions are formed by the coalescence of many emphysematous spaces.

FIGURE 24.18. Close-up view of bullous emphysema (same case as Figure 24.12), showing strands of tissue traversing the areas of emphysematous destruction. These strands represent vascular remnants that were not destroyed.

The morphologic features noted above may apply to any of the forms of emphysema listed in Table 24.2. As outlined in the section on the classification of emphysema, above, these various forms can be distinguished based on their unique characteristics. Centrilobular emphysema, the most common form, tends to involve the upper lobes more severely, and is recognized by the presence of adjacent foci of emphysematous destruction and normal lung. Panlobular emphysema involves the lung more uniformly and tends to be more severe in the lower lung zones. Localized emphysema is characterized by one or at most a few sites of severe emphysematous destruction, with the remainder of the lung essentially normal. Paracicatricial emphysema consists of areas of emphysematous destruction adjacent to scars. The lung may not be enlarged in the latter instance even when the emphysema is severe, because the enlargement due to emphysema is counterbalanced by the shrinkage of the lung due to scarring.[8]

Histologic Findings

The hallmark of emphysema is the finding of air-space dilatation and destruction. Dilatation alone is not sufficient because it may be simply due to overdistention. For example, asthma may be associated with diffuse air-space enlargement secondary to obstruction and hyperinflation. The same process may occur locally secondary to a ball-valve effect, as in the case of some endobronchial tumors or bronchial malformations (congenital lobar emphysema). These hyperinflation conditions should not be confused with or referred to as emphysema.

Alveolar destruction is recognized by the finding of "free-floating" pieces of viable alveolar septa or isolated cross sections of pulmonary vessels (Fig. 24.20). The three-dimensional architecture of normal lung is such that it is not possible to cut a two-dimensional section through the lung without all alveolar septa connecting up with the remainder of the tissue on at least one end. This is true because all normal alveoli consist of intersecting sheets of tissue. With the presence of fenestrations, or holes, in the septa, sections through the sheets can then be cut that appear not to connect up with anything else *in the plane of the section* (they do connect up in the plane above or below). The findings of alveolar space dilatation and free-floating septa are pathognomonic for emphysema. Because of variation due to sampling, it is not possible to estimate the degree or severity of emphysema from histologic sections.

Other histologic findings may also be observed in patients with emphysema. Lesions of the small airways are common (see Chapter 25), since the most common forms of emphysema and small airways pathology are a consequence of cigarette smoking. Pulmonary hypertension secondary to hypoxemia in COPD may result in vascular changes.[42,43] These typically manifest as thickening of the media of small muscular pulmonary arteries, with or without intimal thickening. The more advanced changes of plexiform arteriopathy are not seen in patients with pulmonary hypertension secondary to COPD alone (see Section on Chronic Obstructive Pulmonary Disease in Chapter 28). Pigmented alveolar macrophages are frequently noted, consisting of intraalveolar histiocytes with fine brown cytoplasmic staining (Fig. 24.21). This pigment is due to a combination of kaolin (contaminating the tobacco leaves) (Fig. 24.22), iron (of endogenous origin), and tobacco tars (Fig. 24.23).[44,45] Anthracotic-type pigment may also be observed in the interstitium in association with emphysematous destruction, and the alveoli may be thickened and fibrotic.[46,47]

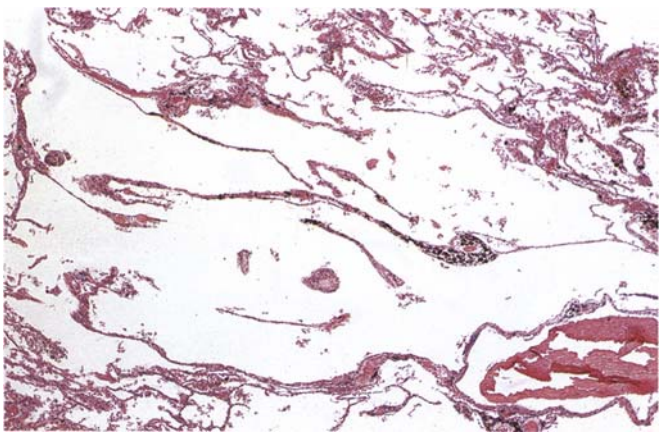


FIGURE 24.20. Histologic appearance of centrilobular emphysema, showing dilatation of air spaces in association with "free-floating" pieces of alveolar septa. Nearly normal lung tissue is present at the lower left.

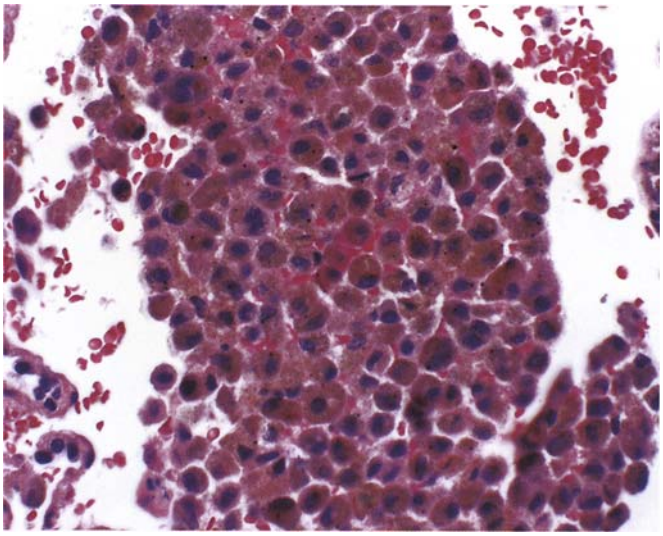


FIGURE 24.21. High-power view of smoker's macrophages demonstrating the typical appearance with fine brown cytoplasmic pigmentation.

Panlobular emphysema is often associated with bronchiolectasia, especially in areas of severe emphysematous destruction.[48] However, the prevalence of bronchiectasis in PLE is variable, with some studies reporting a frequent occurrence and others not (see Chapter 5).[48–51] Finally, in paracicatricial emphysema, there may be evidence of old granulomatous inflammation (healed or active), pneumoconiosis, or other types of scar in association with the emphysematous foci. Granulomatous inflammation in paracicatricial emphysema is commonly related to *Mycobacterium tuberculosis* or *Histoplasma capsulatum* infection. The apical variant of localized emphysema is also frequently associated with areas of fibrosis, often in a subpleural location. This subpleural fibrosis has a granular, somewhat basophilic appearance and has been referred to as an apical pulmonary fibrous cap.[52] The appearance of these caps is due to abundant elastic

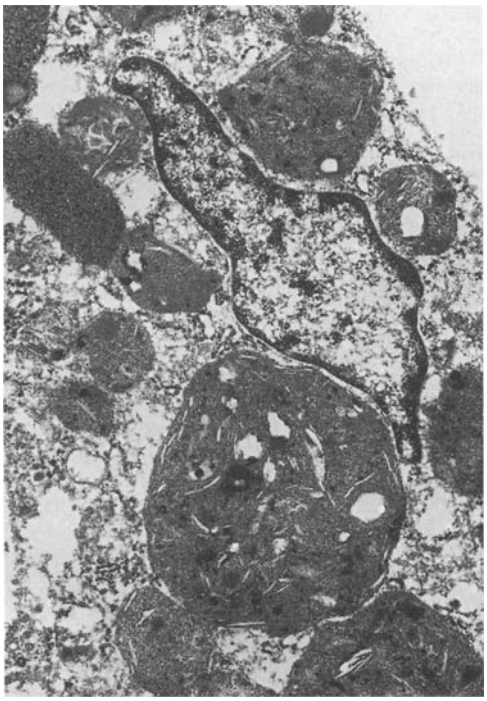


FIGURE 24.22. Smoker's macrophage shows multiple phagolysosomes containing thin, clear-appearing plates of kaolinite. Transmission electron microscopy.

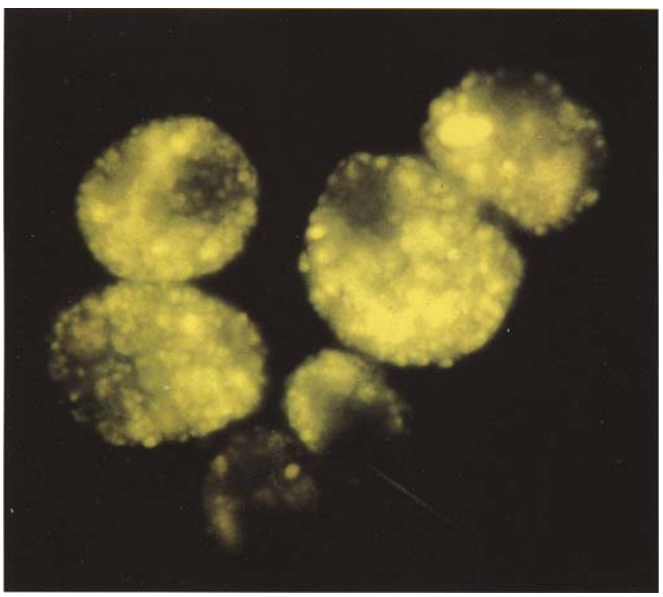


FIGURE 24.23. Fluorescent micrograph of unstained, unfixed smoker's macrophages, showing extrinsic fluorescence. Polycyclic aromatic hydrocarbons and other components of cigarette tars probably contribute to these fluorescent properties. (Courtesy of Dr. John Pauly, Roswell Park Cancer Institute, Buffalo, NY.)

FIGURE 24.24. Pulmonary apical fibrous cap shows abundant elastic tissue representing remnants of collapsed and fibrotic alveoli. (Elastic van Gieson stain.)

fibers (Fig. 24.24), and somewhat resembles radiation pneumonitis, suggesting a vascular origin.[53]

An unusual histologic variant of emphysema is referred to as placental transmogrification of the lung.[54] This variant is associated with giant bulla formation and often occurs in relatively young individuals. The three cases reported by Fidler et al.[54] ranged in age from 24 to 33 years old. The histologic findings include papillary structures containing proliferating blood vessels, lymphoid nodules, smooth muscle, and fat. In some areas, the blood vessels are obliterated by fibrosis. The constellation of histologic findings bears a strong resemblance to placental villi (Fig. 24.25). A rare variant has been described in which there is extensive fat deposition within the alveolar septa. This variant has been referred to as pulmonary lipomatosis.[55]

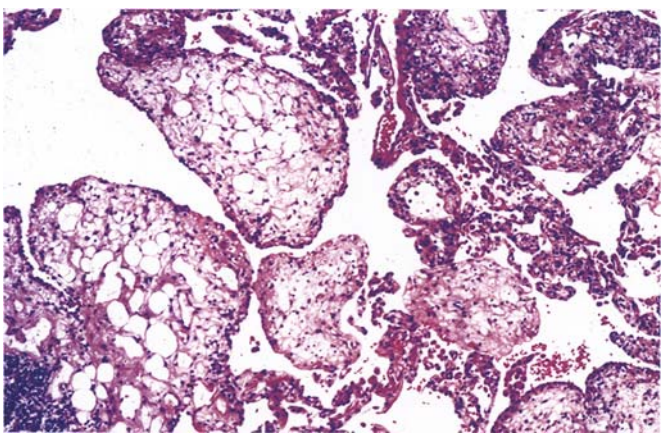


FIGURE 24.25. Placental transmogrification, an unusual variant of bullous emphysema, shows thickened and "free-floating" alveolar septa containing foamy histiocytes. The appearance is reminiscent of placental villi. (Courtesy of Dr. Fred Askin, Johns Hopkins Medical Center, Baltimore, MD.)

Ultrastructure

Transmission electron microscopy shows changes in the alveolar septal wall that may be precursors of the fenestrations described at the light microscopic level. These lesions consist of focal loss of stroma and basal lamina in an intercapillary segment of septum.[56] In these regions, the cytoplasmic membranes of alveolar type I cells from opposite sides of the alveolar septum make direct contact (Fig. 24.26). Sections of actual fenestrations show that they are lined by intact alveolar type I cytoplasm that is continuous from one side to the other. Elsewhere in the lung, the alveolar septa contain a significantly increased amount of elastin and collagen fibers per square micrometer (μm^2) of basal lamina.[47]

Scanning electron microscopy (SEM) shows that the walls of emphysematous spaces may be either thick or thin. The thick walls correspond to foci of fibrosis. The walls of air spaces are lined by alveolar type I and type II epithelium. Occasionally, bronchiolar metaplasia extends into the proximal portion of the emphysematous spaces.[46] The fenestrations observed by examination with the dissecting microscope are readily visualized by SEM (Fig. 24.27).

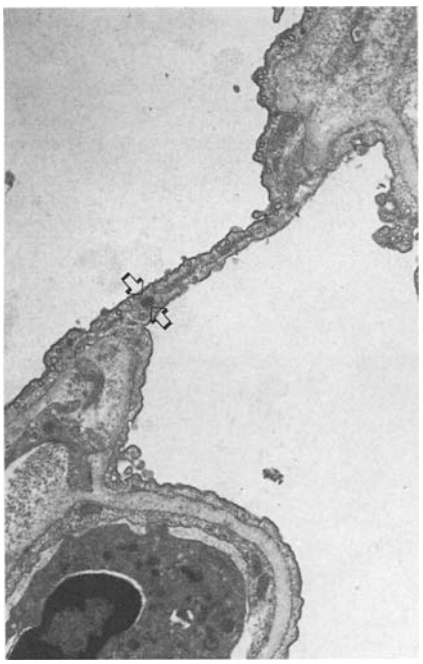


FIGURE 24.26. Transmission electron microscopic view of alveolar septum shows segment in which epithelial basal lamina and other stromal components (collagen, elastic tissue) are absent and type I cells lining two adjacent alveoli are in direct contact. They are actually connected by a desmosomes (between arrows). At top and bottom, all normal components of alveolar septum can be seen, including capillary and leukocyte at bottom. (Courtesy of Dr. T. Takaro, Asheville VA Medical Center, Asheville, NC.)

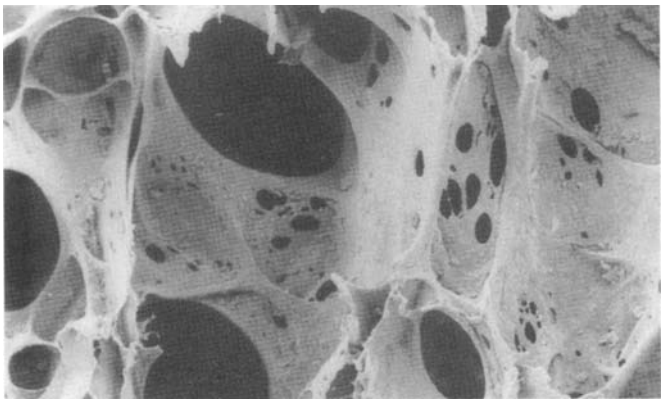


FIGURE 24.27. Scanning electron micrograph of lung shows that the walls of emphysematous spaces are smooth. There are numerous holes in the alveolar septal walls of various sizes and shapes. 48×. (From Nagai and Thurlbeck,[46] with permission. Official Journal of the American Thoracic Society.)

Clinical Correlation

Emphysema causes airflow obstruction, diminished diffusing capacity, and increased lung volumes. Increase in lung volume occurs with mild levels of emphysematous destruction (Fig. 24.19), and is measured clinically by pulmonary function testing (PFT) as an increase in total lung capacity (TLC). This increase in lung volume can also be observed on plain chest films. Four criteria have been proposed for the diagnosis of emphysema on plain chest films: (1) low flat diaphragms on the posteroanterior (PA) chest film, (2) variable radiolucency on the PA film, (3) low flat diaphragms on the lateral chest film, and (4) increased retrosternal clear space on the lateral film (Figs. 24.28 and 24.29). When any two of these criteria are present, clinically significant emphysema (greater than 25% involvement) is usually observed at autopsy.[57] Patients with advanced emphysema often have a barrel chest on physical examination as a consequence of this increase in lung volume.

Emphysema also results in airflow obstruction, which manifests clinically as dyspnea. The mechanism for this airflow obstruction is believed to be due to a loss of the elastic tethering effect of adjacent alveoli on bronchioles. Airflow occurs during exhalation because the pressure in alveoli exceeds that in the lumen of bronchioles.[58,59] At some point, this pressure difference causes the small airways to close, preventing further exhalation. The volume remaining in the lungs is called the residual volume. As the alveolar walls are destroyed by emphysema, there is a decrease in the elastic pull helping to keep the bronchioles open, causing them to close earlier (Fig. 24.30). Consequently, there is a decrease in flow rates as measured by the forced vital capacity (FVC) and

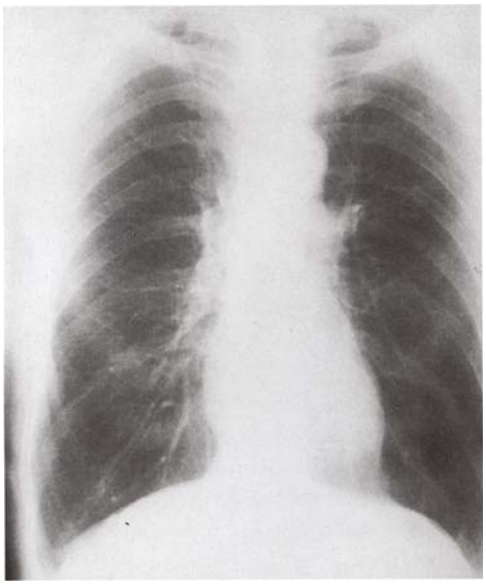


FIGURE 24.28. Posteroanterior chest radiograph in a patient with centrilobular emphysema. The diaphragms are low and flat and there is variable radiolucency.

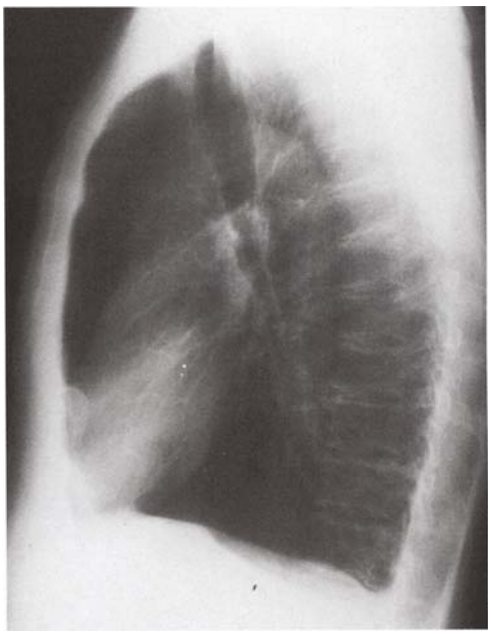
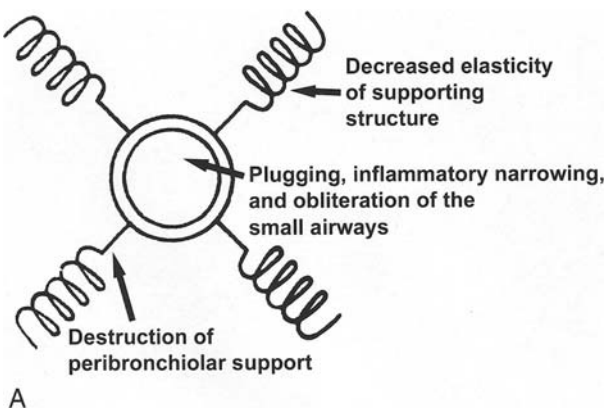


FIGURE 24.29. Lateral chest radiograph in a patient with centrilobular emphysema (same patient as in Figure 24.28). The diaphragms are low and flat and there is enlargement of the retrosternal clear space.

FEV_1, and an increase in residual volume, as measured by PFT.

Emphysema also causes a decrease in the rate of diffusion of oxygen from the alveolar space into the blood. This rate is measured by the diffusing capacity for carbon monoxide (DL_{CO}). The diffusing capacity is a function of the partial pressure of gas across the blood–air barrier, the thickness of the diffusion barrier (alveolar septum), and the total surface area.[60] Destruction of the alveolar septa along with their capillary network causes a loss of surface area (Fig. 24.31), and the decrease in DL_{CO} is proportional to the extent of emphysematous destruction.[61,62] The decrease in diffusing capacity along with ventilation-perfusion mismatch in the lungs of patients with emphysema results in hypoxemia, which further adds to the patient's sensation of dyspnea. Chronic hypoxemia in these patients can result in pulmonary



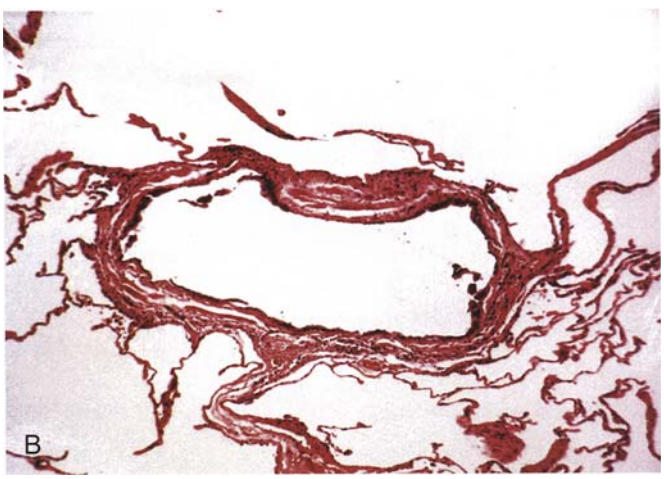


FIGURE 24.30. **A.** Diagram showing the elastic tethering of bronchiolar walls by adjacent alveolar septa. This elastic tethering force is lost as the alveolar walls are destroyed, resulting in early closure of the bronchioles, air trapping, and obstruction to airflow. **B.** Photomicrograph of bronchiole from patient with panlobular emphysema, showing the rupture of alveolar attachments to the wall of this membranous bronchiole. (Courtesy of Dr. Joseph F. Tomashefski, Jr.)

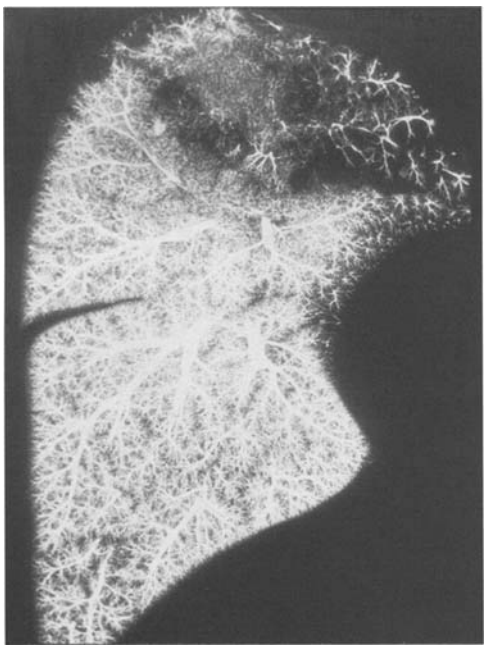


FIGURE 24.31. Intravascular injection corrosion cast of postmortem lung specimen in patient with centrilobular emphysema. Much of the vasculature in the upper lobe has been destroyed by the emphysematous process.

arterial hypertension and eventually lead to cor pulmonale, right-sided heart failure, and death.

With modern high-resolution computed tomography (HRCT), emphysematous destruction can be readily visualized, permitting the diagnosis of preclinical, asymptomatic disease. Foci of emphysematous destruction appear as low-attenuation areas (typically measured in Hounsfield units) without visible walls (Fig. 24.32). Studies have shown that the degree of emphysematous destruction as detected by computed tomography (CT) correlates well with the amount of emphysema measured pathologically.[63–69] The extent of pulmonary emphysema as defined by HRCT also correlates well with reduction in DL_{CO}, but correlates less well with the elastic properties of lung parenchyma.[69] The discrete low attenuation areas typically seen in centrilobular emphysema are not as evident in panlobular emphysema, since the latter process is relatively uniform throughout each lobule and the juxtaposition of normal and emphysematous foci is lacking. In panlobular emphysema, the predominant findings are diffuse pulmonary vascular distortion and pruning.[68]

Localized emphysema is readily identified by HRCT, with an appearance similar to that of centrilobular emphysema but with a more restricted distribution.[68] Patients with localized emphysema are usually asymptomatic and do not have functional impairment. However, when the volume of such a lesion exceeds that of half of a hemithorax, it can reduce the volume available for the normal lung parenchyma to the point that ventilation is impaired.[8] Bullectomy can completely relieve symptoms in such patients. Localized emphysema may also be the cause of spontaneous pneumothorax.[30]

Other clinical correlations of interest have been identified through the study of postmortem inflation-fixed lung specimens and correlating the extent of emphysema with certain clinical parameters. There is an inverse correlation between the extent of pulmonary emphysema and the extent of alcohol consumed.[70] In addition, there is an inverse correlation between death from renal disease and extent of pulmonary emphysema.[71] Pathogenetic factors that may explain these observations are discussed below (see Etiology and Pathogenesis).

In recent years, lung volume reduction surgery has become popular in the treatment of emphysema.[72,73] Removal of emphysematous lung parenchyma permits the expansion of more normal lung tissue to "fill the void," which increases the elastic recoil of the lung and improves the mechanics of ventilation. The patients often experience improvement in dyspnea and exercise tolerance. The pathology of lung volume reduction surgery specimens has been reviewed by Duarte et al.[74] In their series of 65 specimens, the histologic grade of emphysema was mild in 9%, moderate in 72%, and severe in 19%. Other significant pathologic findings in these specimens, in addition to emphysema, included adenocarcinoma (in three specimens), granulomatous bronchiolitis and pneumonitis (one), inactive aspergilloma (one), bronchiolitis (54), bronchiolectasis (six), and bronchoalveolar metaplasia (one). Incidental findings included interstitial fibrosis and scar (55), interstitial inflammation (20), calcification (20), ossification (11), bone marrow emboli (four), chemodectoma (two), and carcinoid tumorlets (one).

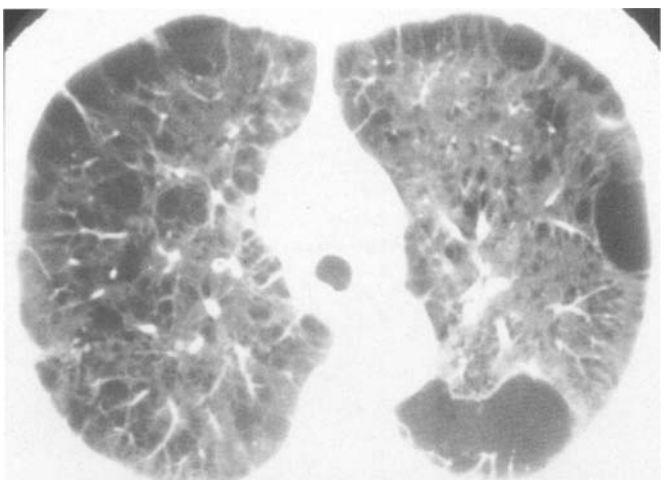


FIGURE 24.32. Computed tomographic scan of the thorax in a patient with centrilobular emphysema, showing multiple low-attenuation areas characteristic of this disorder.

TABLE 24.3. Prevalence and mean extent of centrilobular emphysema (CLE)

Group	*n*	Age (years)	CLE (%)[a]	CLE (%)[b]	Mean % of CLE[c]
All	565	56.5	37.2	13.5	24.9
All smokers	460	56.3	42.2 ($p < .0001$)[d]	16.3 ($p < .0001$)	26.4 ($p < .0001$)
Nonsmokers	105	57.3	16.2 ($p < .0001$)	1.0 ($p < .0001$)	6.7 ($p < .0001$)
Cigarette smokers	427	55.6	43.6 ($p < .05$)[e]	16.9 ($.05 < p < .10$)	26.6 ($p < .5$)
Pipe/cigar smokers	33	65.1	24.2	9.1	23.0

[a]Prevalence of lungs with trace or more of CLE.
[b]Prevalence of lungs with 25% or more of CLE.
[c]Mean content of CLE in all cases with CLE.
[d]Probability values are located between the items compared.
[e]Probability for nonsmokers versus pipe/cigar smokers is same as this.

Lung transplantation is also frequently employed for selected patients with end-stage lung disease due to emphysema.[75] Consequently, surgical pathologists are more likely to encounter lung specimens with emphysema, and there is an enhanced opportunity for clinical and pathological correlations.

Etiology and Pathogenesis

Cigarette smoking is by far the most common etiologic agent for emphysema.[15,16] In a study of 565 cases with inflation-fixed lung specimens and available smoking history, the prevalence of emphysema in 427 cigarette smokers was found to be 43.6% (Table 24.3). The mean extent of emphysema was 16.9%, and among those who had any detectable emphysema, the mean extent was 26.6%. This means that of those smokers with any detectable emphysema, symptomatic COPD would be present in about half, since 25% destruction is the level at which symptomatic COPD typically appears.[8] In contrast, the prevalence of emphysema in 105 nonsmokers was 16.2%, with a mean extent of 1.0% (Table 24.3). Only one case of an alleged nonsmoker had as much as 25% emphysematous destruction of lung parenchyma. The prevalence of emphysema among 33 pipe or cigar smokers was 24.2%, and among those with any detectable emphysema, the mean score was 23.0% (Table 24.3). The latter value was not significantly different from that of cigarette smokers, indicating that pipe or cigar smokers who inhale develop emphysema to an extent similar to that of cigarette smokers.[8] The study further showed evidence of a dose-response relationship (Table 24.4).[8]

Two independent observations were key to our current concepts of the pathogenesis of emphysema. The first was the discovery of deficiency of α_1–antitrypsin in several Swedish families with severe emphysema.[76] The second was the development of emphysema in experimental animals treated with intratracheal instillation of crude papain.[77] Together, these observations led to the protease-antiprotease concept of the pathogenesis of emphysema.[78]

Subsequent studies identified leukocytes as the major source of proteases in the development of emphysema (Fig. 24.33). The primary culprits appear to be elastase produced by neutrophils[79–81] and metalloproteinases produced by macrophages.[82,83] There is also evidence that macrophages secrete an enzyme with elastase-like activity.[84] Elastin and other matrix components of the alveolar septum are degraded by these enzymes, resulting in destruction of alveolar tissue. Reactive oxygen species, including superoxide radical, hydrogen peroxide, and hydroxyl radical, may also be involved in the matrix degradation.[80]

Cigarette smoking upsets the normal balance between proteases and antiproteases by producing a particulate and oxidant stress on the lung that results in an influx of inflammatory cells. Both macrophages and neutrophils are present in increased amounts in the lungs of smokers.[79] Experimental studies suggest that smoke-induced connective-tissue breakdown requires both neutrophils and macrophage metalloelastase.[85] Increased elastase activity is present within bronchoalveolar lavage fluid from smokers,[81] and smokers macrophages produce elevated quantities of matrix-degrading enzymes with both elastolytic and collagenolytic activities in vitro.[83] The balance is

TABLE 24.4. Effect of smoking on prevalence and extent of centrilobular emphysema (CLE)

Group	*n*	Mean age	CLE (%)[a]	Mean % of CLE[b]
All	469	55.5	42	9.7
Nonsmoker	95	57.1	18	1.7
Moderate smoker[c]	210	55.3	48	12.6
Heavy smoker[d]	76	54.4	61	16.5
Unknown[e]	88	55.8	38	5.8

[a]Prevalence of any degree of CLE.
[b]Average of measured extent (%) of CLE for all cases in group, counting each case without emphysema as "0."
[c]10–30 cigarettes per day.
[d]More than 30 cigarettes per day.
[e]Smoking history not recorded in clinical chart.

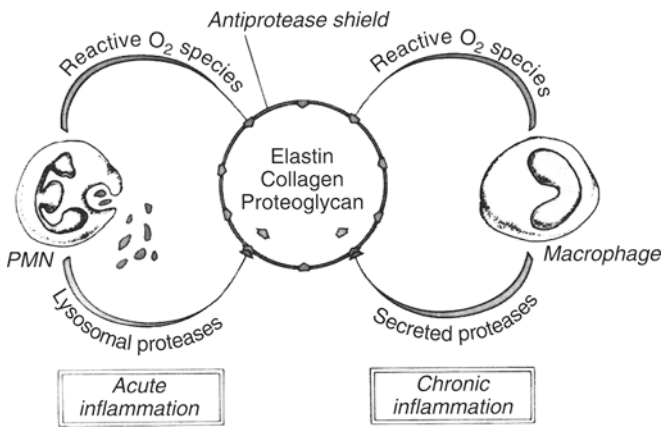


FIGURE 24.33. Proposed pathway of tissue injury in a microenvironment of inflammatory cells. Hypothetical scheme for exacerbation of protease-mediated tissue injury by reactive oxygen species liberated from polymorphonuclear neutrophils (PMNs). Phagocytosis of immune complexes by the cells leads to simultaneous release of granule-associated proteolytic enzymes and formation of activated species of oxygen, including superoxide radical, hydrogen peroxide, and hydroxyl radical. The reactive forms of oxygen inactivate antiproteases, such as α_1-protease inhibitor, in the microenvironment of the cells, thus allowing leukocytic proteases to more readily attack adjacent connective tissue structures. (From Kuhn and Senior,[79] with permission.)

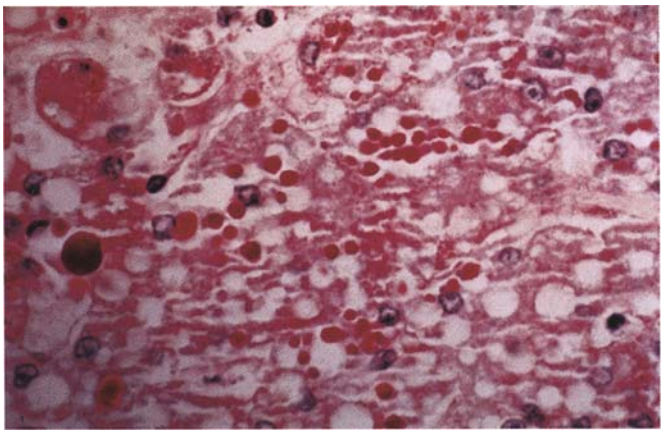


FIGURE 24.34. Histologic section of liver in patient with Pi Z type of α_1-antitrypsin deficiency, showing periodic acid-Schiff (PAS)-positive globules within the cytoplasm of hepatocytes. (PAS.)

further tipped in favor of proteases in that cigarette smoke oxidizes the serine active site of α_1–antitrypsin, thereby inactivating the enzyme.[86] Furthermore, synthetic serine elastase inhibitor reduces cigarette smoke–induced emphysema in a guinea pig model.[87] There is also evidence that mechanical forces may be important in the progressive nature of emphysema.[88]

α_1-Antitrypsin is a glycoprotein with a molecular weight of 52 kDa that is synthesized in the liver. At least 75 genetic variants have been identified as determined by isoelectric focusing in polyacrylamide gels.[89,90] The most common type is protease inhibitor (Pi) M, and the allele products are codominant. The most common variant associated with α_1–antitrypsin deficiency is Pi Z, an electrophoretically slow migrating variant resulting from a mutation in which lysine is substituted for glutamic acid in residue 342.[91] Individuals homozygous for the Z-allele have 10% to 15% of the normal serum level of α_1–antitrypsin.[89] This reduction in serum activity is a consequence of amino acid substitution, which prevents the attachment of the carbohydrate side chain.[89,90] As a result, the glycoprotein accumulates within hepatocytes and can be readily identified with periodic acid-Schiff (PAS) staining (Fig. 24.34). At the ultrastructural level, the amorphous electron dense material can be shown to accumulate within the rough endoplasmic reticulum of hepatocytes (Fig. 24.35).

The organs most commonly affected in α_1–antitrypsin deficiency are the liver and the lung. Periodic acid-Schiff–positive globules may be identified in hepatocytes of individuals who are either homozygous or heterozygous for the Pi Z allele.[89,92,93] This manifests as neonatal hepatitis or cirrhosis in homozygous individuals, primarily in childhood.[89] There is some evidence that heterozygotes for the Z-allele may be at increased risk for cirrhosis as adults.[92,93] Homozygotes also develop panlobular

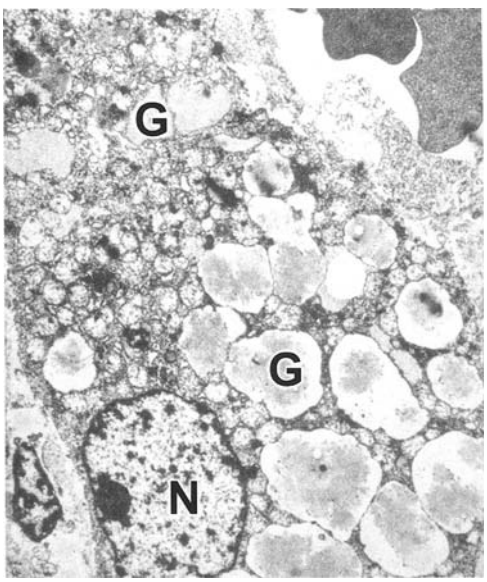


FIGURE 24.35. Transmission electron micrograph of liver in patient with α_1-antitrypsin deficiency. Multiple profiles of rough endoplasmic reticulum are dilated with flocculent electron dense material, correlating with PAS-positive globules observed by light microscopy. G, globules; N, nucleus.

emphysema, usually becoming symptomatic during the fourth or fifth decades.[48,94] Individuals who also smoke cigarettes have onset of symptoms at a younger age, more severe airflow obstruction, an increased rate of airflow decline over time, and a shorter life expectancy.[95,96] There is also evidence that occupational exposure to dust, fumes, smoke, or gas is associated with respiratory symptoms and airflow limitation in individuals with α_1–antitrypsin deficiency.[97] There is no convincing evidence that heterozygotes for the Z-allele are at risk for panlobular emphysema.

The pathogenetic mechanism for liver injury in α_1–antitrypsin deficiency is unclear, although the insoluble nature of the protein precipitate within hepatocytes is an important factor.[90] The proposed mechanism of emphysema is the unopposed action of neutrophil elastase in the face of diminished circulating levels of α_1–antitrypsin. The lung is believed to be the "graveyard" for neutrophils, which release proteases (including elastase) from their granules at the time of cellular death. Investigators have demonstrated that the Z variant of α_1–antitrypsin forms polymers that are chemotactic for neutrophils.[91] These polymers may form within the lung from the low levels of circulating α_1–antitrypsin in these patients and may thus exacerbate the neutrophil elastase burden within the lung. Treatment includes administration of recombinant α_1–antitrypsin as well as lung transplantation.[75] Recurrence of emphysema in the transplanted lung has been reported.[98]

The distribution of disease in patients with CLE and PLE also supports the protease-antiprotease hypothesis. In cigarette smokers with normal levels of α_1–antitrypsin, the disease is worse in the upper lobes because of the greater blood flow (and hence more antiprotease delivered) to the lower lobes. Particulate matter tends to accumulate in a perivascular and peribronchiolar distribution, which is consistent with the centrilobular nature of emphysema in cigarette smokers.[8] In addition, particle removal by lymphatics is likely to be less efficient in the upper lobes due to relatively less blood flow. In patients with α_1–antitrypsin deficiency, the disease is worse in the lower lobes because of the greater blood flow (and hence more neutrophils delivered). Furthermore, greater blood flow would result in more polymerized antiprotease in the lower lobes (and hence greater neutrophil chemotaxis).[91] Finally, the even distribution of emphysema throughout the lobule is consistent with uniform capillary blood flow throughout the individual pulmonary acinus or lobule.

Panlobular (panacinar) emphysema has also been reported as a complication of intravenous drug abuse.[99,100] Schmidt et al.[99] studied seven autopsied cases of individuals who were intravenous Ritalin abusers with profound obstructive lung disease. Talc granulomas were identified within the lung parenchyma, and α_1–antitrypsin deficiency was excluded in five autopsied cases that were tested. The mechanism remains to be elucidated, but may be related to localized protease-antiprotease imbalances around the innumerable granulomas (see Chapter 26).

Further support for the protease-antiprotease concept derives from autopsy studies of formalin inflation-fixed lung specimens. Studies conducted by Pratt and Vollmer[70] demonstrated that alcohol consumption decreases the prevalence and extent of CLE in a dose-dependent manner (Table 24.5). A proposed mechanism for this effect comes from studies of patients admitted with acute alcohol intoxication, whose neutrophils were found to have about half of the normal levels of elastase. This effect was reversed by the completion of detoxification.[101] Another interesting observation relates to the finding of low levels of emphysema in patients dying from renal failure.[71] The injured kidney releases renin, which stimulates production of angiotensin I by the liver. Angiotensin I is converted to angiotensin II within the capillary bed of the lung, which increases blood pressure, further injuring the kidney. Destruction of the pulmonary capillary bed by emphysema decreases the efficiency of conversion of angiotensin I to angiotensin II, ameliorating further injury to the kidneys. Thus, according to this hypothesis, patients with substantial amounts of emphysema would be less likely to die from end-stage renal disease.[71]

The mechanism of emphysema production in localized and paracicatricial types is less well understood. It is possible that some forms of localized emphysema (see Fig. 24.11) may be related to prior bacterial infections. It is well recognized that *Pseudomonas aeruginosa*, for example, produces both elastase and alkaline protease. Furthermore, there is evidence that *P. aeruginosa* can inactivate α_1–antitrypsin.[102] Apical forms of localized (paraseptal) emphysema may be aggravated by mechani-

TABLE 24.5. Effects on alcohol consumption on prevalence and extent of centrilobular emphysema in smokers

			Prevalence of CLE		Mean % of CLE	
Alcohol use	*n*	Age	Trace or more	More than 25%	All cases	Cases with CLE
None	57	59	56.1	25.9	16.9	30.2
Slight to moderate	59	58	52.5	17.0	12.2	23.1
Heavy	57	55	35.1	10.5	8.6	24.6
Mean	173	57.3	47.9	17.8	12.6	25.9

cal stress from the weight of the subjacent lung.[8] It is also possible that decreased perfusion of the lung apex (and hence less antiprotease delivered) may be a contributing factor. Mechanical stress may also be operative in paracicatricial emphysema.[88] The role, if any, of the Pi MZ heterozygous state, which results in α_1–antitrypsin levels intermediate between Pi Z homozygotes and normal (Pi M) individuals, in any of these less well understood disorders is unknown.

Recent studies have examined gene expression profiling in order to try to better understand pathogenetic mechanisms in emphysema.[103,104] Emphysematous tissue showed a global decrease in gene expression as well as an increased abundance of transcripts encoding proteins involved in inflammation, immune response, and proteolysis. Significant differences in modulation of groups of genes associated with protein and energy metabolism and immune function were observed when centrilobular emphysema was compared to panlobular emphysema. There was also evidence that gene expression profiles may predict response to lung volume reduction surgery and identify targets for therapeutic intervention.

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