SIX

Chronic Obstructive Pulmonary Disease

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Emphysema

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Although much has been learned about emphysema in the past forty years, it is certainly not a new disease. Dr. Samuel Johnson (1709–1784), the eminent English lexicographer and author, alluded in many of his letters to symptoms of his chronic respiratory disease. This disease was emphysema, as confirmed at necropsy and depicted in Baille's anatomic atlas.[1] Laennec, in the early 1800s, made astute observations on emphysema; notably, he urged the inflation of lungs for a better study of the disease.[2] Perhaps Laennec's advice went unheeded, because for the following 150 years, the study of emphysema advanced little beyond histologic descriptions and definitions. An awakening of interest came about in the late 1950s and progressed rapidly with a consensus definition,[3–5] accurate morphology,[6–10] and the use of morphometry[11] to provide pathologists, clinical investigators, physiologists, and biochemists a solid foundation for further research on emphysema.

Emphysema was also separated from other chronic diseases that produce limitation to airflow, mainly chronic bronchitis. The term "chronic obstructive pulmonary disease" (COPD), which is comparable to chronic obstructive lung disease, or chronic airflow obstruction, embraces varying combinations of emphysema and airway disease. Because the two cannot be reliably separated in most living patients, the use of COPD is justifiable. Asthma and bronchiectasis are also considered part of the COPD syndrome.[9,12]

Major advances in morphologically defining emphysema have resulted from the use of endobronchial inflation of the lung with formalin or formalin steam, thus restoring the lung to a volume attained during life and fixing it in such state for proper gross and microscopic examination. The ideal setup for lung inflation consists of a formalin bath to hold the lung and a reservoir fed by a pump, which allows continuous endobronchial inflation at a specified pressure (see Chap. 5).[13,14] However, filling the lung to an approximation of total lung capacity, clamping the main bronchus, and letting it fix in a bath of formalin for a few hours is quite adequate for routine pathology, although fixation for a day or two provides better specimens. Parasagittal sectioning (*i.e.*, slicing in the plane of a lateral chest film) best shows emphysema, especially if the slice of fixed lung is floated in a tray of water and examined under good illumination.

Scientists have moved beyond morphology in the study of emphysema and can identify many of the molecular and biochemical events that produce the lesion, including the genetic aberrations responsible for its occurrence in certain individuals (see Pathogenesis). However, morphology still remains a fruitful way to begin to understand emphysema, and provides a basis for additional research.

DEFINITIONS AND RELATED TERMS

The consensus definition of emphysema is "a condition of the lung characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by the destruction of their walls, and without obvious fibrosis."[5] Emphysema is thus part of a larger set of conditions characterized by respiratory airspace enlargement that are outlined in Display 26-1. Both normal and abnormal air spaces are distal to the terminal bronchiole within the acinus and include respiratory bronchioles, alveolar ducts, and alveolar sacs. Respiratory air-space enlargement is defined as "an increase in airspace size as compared with the airspace of normal lungs. The term applies to all varieties of airspace enlargement distal to the terminal bronchioles, whether occurring with or without fibrosis or destruction."[5] A better understanding of emphysema can be achieved by examining each part of the definition.

Note that the air-space enlargement of emphysema is abnormal; thus, the condition of senile emphysema, a result of normal aging, does not fit the definition of emphysema. Emphysema is also characterized by permanent enlargement of air spaces, which implies that it is an irreversible condition. As would be expected in a permanent change, there is destruction of the alveolar walls. Another consensus was reached for the definition of destruction: "nonuniformity in the pattern of respiratory airspace enlargement

DISPLAY 26-1. RESPIRATORY AIR SPACE ENLARGEMENT

Simple air space enlargement
- Congenital
- Acquired

Emphysema
- Centriacinar
  - Centrilobular (*i.e.*, proximal acinar)
  - Focal (*i.e.*, dust)
- Panacinar (*i.e.*, panlobular)
- Paraseptal (*i.e.*, perilobular, distal acinar, or subpleural)
- Irregular (*i.e.*, paracicatricial or scar)
- Bulla

Air space enlargement with fibrosis (*i.e.*, honeycombing)

Adapted from Snider GL, Kleinerman J, Thurlbeck WM, Bengali ZH. Report of a National Heart, Lung, and Blood Institute, Division of Lung Diseases, Workshop. The definition of emphysema. Am Rev Respir Dis 1985;132:182.

so that the orderly appearance of the acinus and its components is disturbed and may be lost."[5]

Because emphysema lesions occur distal to the terminal (*i.e.*, last nonrespiratory) bronchiole, they do not directly involve the conducting cartilaginous bronchi and are limited to the acinus or gas-exchanging alveolated portion of the lung. Although many destructive diseases, especially chronic ones, are characterized by fibrosis, emphysema is not. This remarkable difference from other chronic diseases is perhaps explained by the subtlety of the destructive changes taking place over decades and the peculiar mechanisms of tissue destruction in this disease (see Pathogenesis).

A brief look at other conditions of respiratory air-space enlargement that are not emphysema will put the definition of emphysema into even sharper focus. Congenital simple air-space enlargement can be seen in conditions such as pulmonary hypoplasia or congenital lobar overinflation; the latter has been misnamed "lobar" emphysema.[15–17] Also, in bronchopulmonary dysplasia, septation of saccular air spaces into well-formed alveoli may not take place or may be retarded, resulting in enlarged air spaces that look microscopically like emphysema.[18] This form of air-space enlargement is not so much destruction of preexisting air spaces as it is lack of development of air spaces of normal size.

Acquired simple air-space enlargement is also nondestructive and can be seen in the contralateral lung after pneumonectomy, in compensatory emphysema, or in other conditions that cause hyperinflation or overdistention of the lung. Portions of the gas-exchanging area of the lung dilate with increasing age, particularly alveolar ducts, and this change has been called "senile" emphysema.[19] As noted, it is a part of the normal aging process; therefore it should be called aging lung (see Chap. 2).

Destructive air-space enlargement with fibrosis is frequently called "honeycombing," and although it may appear similar to emphysema at the gross level, fibrosis is obvious microscopically. Honeycombing is a feature of end-stage fibrosing alveolitis or other chronic interstitial diseases, and its resemblance to emphysema is superficial (see Chaps. 31 through 33).

Neither interstitial emphysema nor subcutaneous emphysema are emphysema at all by the above definition; because they do not involve air spaces, they do not represent respiratory air-space enlargement. The appropriate term for these two conditions is simply "air." Interstitial air dissects secondary lobules, bronchovascular bundles, and the pleura, usually as a result of barotrauma (Color Fig. 26-1). Subcutaneous air usually represents an extension of interstitial emphysema following intrathoracic barotrauma.

TYPES OF EMPHYSEMA

There are five generally recognized types of emphysema (see Display 26-1): centriacinar (*i.e.*, centrilobular, proximal acinar), panacinar (*i.e.*, panlobular), paraseptal (*i.e.*, perilobular, distal acinar, subpleural), irregular (*i.e.*, paracicatricial, scar), and bullous (Fig. 26-1). All of these fit the definition of emphysema described above. Centriacinar emphysema is by far the most common type, but panacinar emphysema is also an important disease; bullae can be clinically significant. The remaining two forms of emphysema, paraseptal and irregular, are of lesser clinical importance.

Emphysema lesions share certain histologic features, irrespective of their type. They measure 1 to 10 mm in diameter. An emphysema lesion that is larger than 10 mm is a bulla. The size of the largest nonbullous emphysema lesion is, therefore, approximately the size of an acinus.

Fibrosis, as stated previously, is essentially absent from emphysema lesions, although bullae, because of their usual subpleural location, include the fibrous tissue of the pleura in a portion of their wall. Thin strands of fibrous tissue, sometimes called baffles, may subdivide an emphysema space into smaller chambers. The wall of an emphysema lesion is often as thick as an alveolar wall, or not more than twice as thick. An *en face* view of the alveolar septa would show a great loss and irregular spacing of alveolar capillaries, unlike the dense, uniform capillary meshwork of normal lung. Walls of emphysema lesions contain fenestrae or windows between air spaces, which may measure up to 75 μm and average 13 μm in diameter.[20] These are much larger than the normal interalveolar pores of Kohn. Although this capillary destruction is not easily appreciated in routine histologic preparations, destruction can be assumed by the absence of alveolar septa protruding

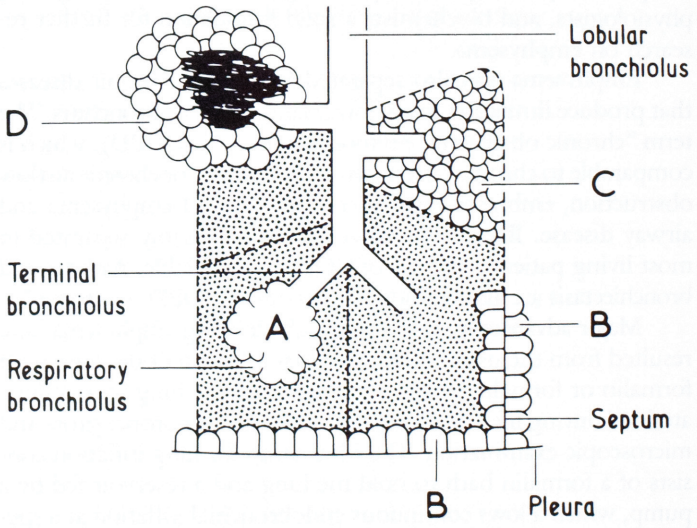

FIGURE 26-1. Anatomic types of emphysema are centriacinar or centrilobular (A), periacinar or paraseptal (B), panacinar (C), and irregular or scar (D). The acinar boundary is indicated (*dashed lines*). Generally, a connective tissue septum is not present; therefore, collateral ventilation can occur. (From Reid LM. Chronic obstructive pulmonary diseases. In: Fishman AP, ed. Pulmonary diseases and disorders. New York: McGraw-Hill, 1988:1247.)

into an emphysema lesion, unlike the appearance of the normal acinus.

In addition to the size of individual lesions, grades of severity of emphysema can be described based on the percent surface area of lung involved on gross examination. Minimal emphysema is diagnosed when only a few lesions are present, and it involves less than 1% of the lung. Mild emphysema involves up to 10% of the lung; moderate emphysema involves from 10% to 25% of the lung; moderate-to-severe emphysema involves from 25% to 50% of the lung; and severe emphysema involves over 50% of the lung. A series of panels of gross pictures of parasagittal slices of lung showing increasing severity of emphysema have been used to streamline analysis of gross emphysema.[21–23] These panels are prepared from thin slices of lung mounted on paper (*i.e.*, the Gough technique)[24] and are graded from 0, which indicates that no emphysema is present, to 100, which indicates the worst example of emphysema identified. These grades do not correspond directly to absolute percentages. Both extent of emphysema and severity of individual lesion can be estimated by choosing appropriate panels.[21–24]

Centriacinar Emphysema

Centriacinar emphysema lesions involve primarily respiratory bronchioles. They are located in the approximate center of the acinus and are surrounded by normal alveolar ducts and sacs,[25,26] as seen in Figure 26-2. Four to nine acini together make up a pulmonary lobule, which measures a few centimeters in diameter in the adult lung and is partially bounded by intralobular septa. Thus, a centriacinar lesion anatomically tends to be centrilobular. Sections from lungs with mild emphysema will show the centriacinar pattern best. Smaller lesions may be recognized microscopically, but evidence for destruction will be slight, and lesions much smaller are the same size as a dilated alveolar duct, which is about 0.7 mm in diameter.

Lesions larger than 1 cm can destroy the entire acinus; these would be classified as bullae.[4] The centriacinar location of the lesion is documented by the presence of a small muscular artery that accompanies the preexisting respiratory bronchiole. Black atmospheric pigment typically collects in this zone of the lung, so the lesion is frequently pigmented black. Not only is the lesion surrounded by a rim of normal alveolar tissue, but alveolar ducts can be seen opening into the centriacinar lesion.

Grossly, centriacinar emphysema lesions favor the upper one half of the lung. They are sharply defined holes without a discernible wall and are surrounded by normal lung parenchyma (Fig. 26-3). If interlobular septa are apparent, one or more lesions may be seen within the secondary lobule. The lingula or the right middle lobe of the lung may be relatively spared, but the superior segment of the lower lobes is often involved. Thus, a lung may have only a few centriacinar emphysema lesions a few millimeters in diameter each, or in the most severe cases it may be riddled with lesions, most of which approach the 1-cm diameter size, even extending to the diaphragmatic surface.

One classification further breaks down centriacinar emphysema into centrilobular and focal.[5] Centrilobular is an old synonym employed largely to distinguish the lesions caused by cigarette smoking from the focal emphysema associated with coal and other mineral dust exposures. Usually, the term "centriacinar" is used to mean non–dust-related, as opposed to "focal" or "dust-related" centriacinar emphysema. Focal emphysema therefore is classified with simple coal worker's pneumoconiosis or small-airway dust lesions (see Chap. 34).

Panacinar Emphysema

This form of emphysema is one twentieth as common as centriacinar emphysema but is still recognized fairly frequently. Panacinar emphysema due to α_1-antitrypsin (AAT) deficiency is not morphologically different from that due to other causes.[27,28] The entire acinus, from respiratory bronchiole to alveolar sac, is involved by emphysematous air spaces. Where lobules are bounded by pleura or interlobular septa, the lesions abut these structures. Microscopically, a pattern of thin air-space walls with few protruding septa is seen with one abnormal air space next to the other, without a surrounding zone of normal alveolar parenchyma (Fig.

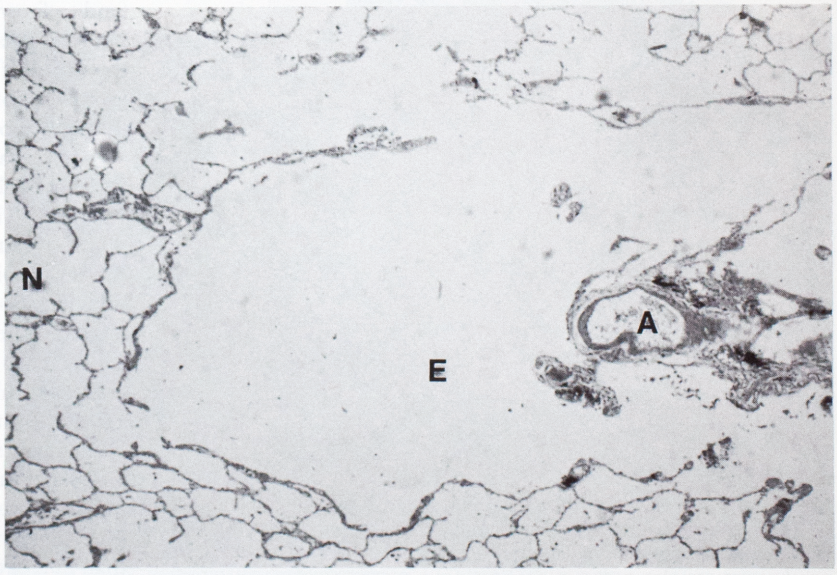

FIGURE 26-2. Histology of centriacinar or centrilobular emphysema. The lesion (E) is surrounded by normal parenchyma (N). A small muscular artery (A) is adjacent to the remnants of a respiratory bronchiole. (H & E stain; low magnification.)

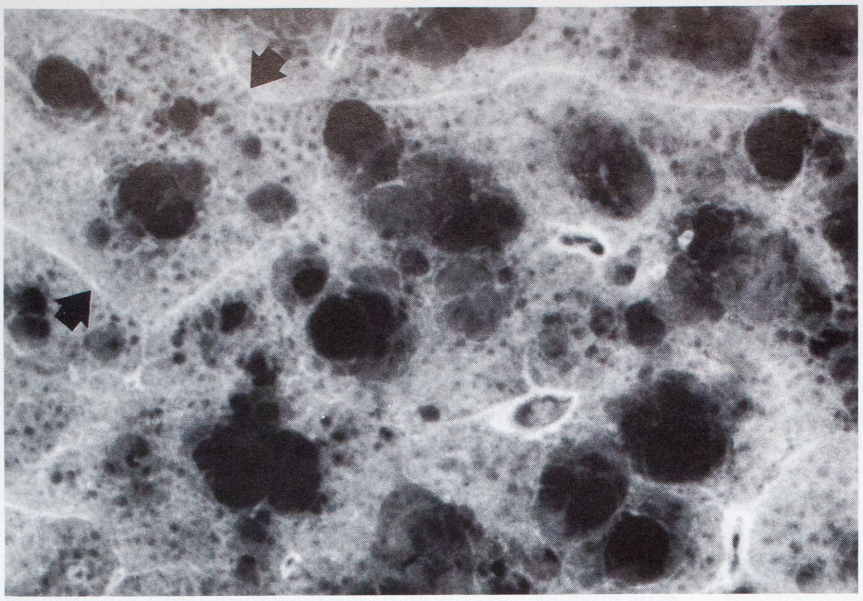

FIGURE 26-3. Gross appearance of centriacinar emphysema. The dark, punched-out lesions are surrounded by normal lung. Interlobular septa can be seen (*arrows*).

26-4). Again, fibrosis is essentially absent. Location in the acinus is difficult to ascertain microscopically because of the diffuseness of the lesion, unless there are intralobular septa.

Grossly, panacinar emphysema diffusely involves the lower one half or the entire lung (Fig. 26-5). A pattern of enlarged air spaces, again in the 1- to 10-mm size range of centriacinar emphysema, is present but occurs without a surrounding rim of normal lung parenchyma. Although only one acinus in a pulmonary lobule may be involved, the entire lobule is more typically involved, as depicted in Figure 26-6. Sometimes the panacinar lesions do not have excess atmospheric pigment and average only a few millimeters in diameter, yet they have a severe grade of functional involvement. Recognition of the extensiveness of the lesions may be appreciated by floating a slice of the endobronchially formalin-inflated lung in water and lifting the slice out of the water from below. An emphysematous lung will collapse and resemble a wet rag, whereas a normal lung will maintain its shape and porous character.

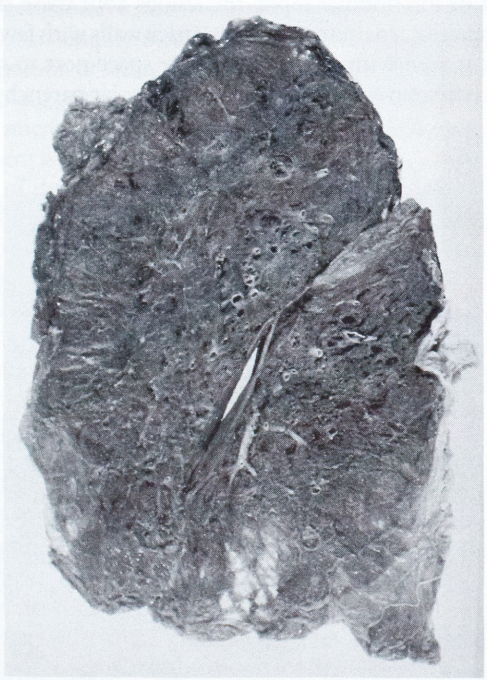

FIGURE 26-4. Sagittal section of the lung in a young man with α_1-antitrypsin deficiency. Panacinar emphysema was present throughout the lungs but was more severe in the lower lobes. Small foci of centrilobular emphysema are also noted at the apex. The patient smoked cigarettes. (Contributed by the editor.)

Other Forms of Emphysema

Paraseptal emphysema involves the distal part of the lobule (*i.e.*, the alveolar ducts and sacs) rather than the respiratory bronchioles. The lesions occur next to interlobular septa, and subpleurally, or even next to bronchovascular bundles. The microscopic appearance reflects the distal acinar location.[29] Grossly, the abnormal air spaces are usually 5 mm or less, and the degree of lung involvement is mild (see Fig. 26-6*A*). The subpleural lesions tend to favor the upper one half of the lung, but other lesions are randomly distributed. Because extensive lung involvement is rare, this form of emphysema does not usually produce symptoms. However, some cases of spontaneous pneumothorax may be due to rupture of subpleural lesions.

Irregular emphysema is a form of emphysema that has the typical histologic appearance of emphysema and the typical 1- to 10-mm size but does not have any predictable relationship to the acinus. Often it occurs adjacent to areas of scarring (Fig. 26-7). Areas of typical air-space enlargement can occur around nodular scars in the lung. The distribution of these lesions depends on the scar, and the process is usually minimal to mild.

A bulla by definition is greater than 10 mm in diameter. Typically, bullae occur in the upper lobe of the lungs at the apex or along the sharp margins, particularly anteriorly, but they may occur at any site subpleurally or even deep within the parenchyma. Grossly, a bulla bulges out into the pleural space in most cases, rather than occurring deep within lung tissue, as shown in Figure 26-8. The protruding wall of a bulla appears to be slightly thicker than that of a typical emphysema lesion because a subpleural bulla will incorporate the pleura into its wall (Fig. 26-9), and when

FIGURE 26-5. Histology of panacinar emphysema in a patient with α_1-antitrypsin deficiency. Enlarged air spaces with few protruding alveolar septa are seen. (H & E stain; low magnification.)

expanding within the lung it incorporates collapsed intralobular septa.

Occasionally, a bulla may also have strands of connective tissue and residual blood vessels transversing it. Bullae should not be thought of as simply an outpouching of the pleura. The base of a subpleural bulla extends down into the lung, and there is destruction of lung tissue as well. Reid has described three types of communication of bullae with the rest of the lung: narrow-necked, broad-based and superficial, and broad-based and deep.[2] Bullae may coexist with the other forms of emphysema mentioned or may be the predominant form of emphysema in the lung (*i.e.*, bullous emphysema). Likewise, they may be single, thus being an incidental finding, or so numerous that they do not allow adequate expansion of the lung parenchyma and require surgical removal. The success of that surgical removal is, in great part, dependent on the degree of emphysema in the underlying lung tissue.

The term "bleb" has been used by many to denote a small bulla, but its true meaning is an intrapleural collection of air.[3] Thus, a bleb is a localized pocket of interstitial emphysema typically subpleural with no element of destruction of lung tissue.

Although the above classification should clearly distinguish the various forms of emphysema, in practice many difficulties arise. First of all, the definitions of the various distributions and the appearance of the emphysema lesions are evident in mild degrees of emphysema; in moderate to severe disease, those distinctions become blurred. Although it is tempting to designate a lung involved with emphysema as a single type, a mixture of several types is often present. Some centriacinar emphysema lesions are so large that the rim of normal tissue surrounding them is barely seen and inconstant; they would thus qualify as panacinar lesions.

In fact, the lungs of a typical patient dying of end-stage severe emphysema will show so much air-space enlargement that it is difficult to categorize the type of emphysema. Such morphologic difficulty has prompted the question of whether centriacinar and panacinar emphysema are different diseases. Clinically and physiologically they are remarkably similar, but if morphology fails, the

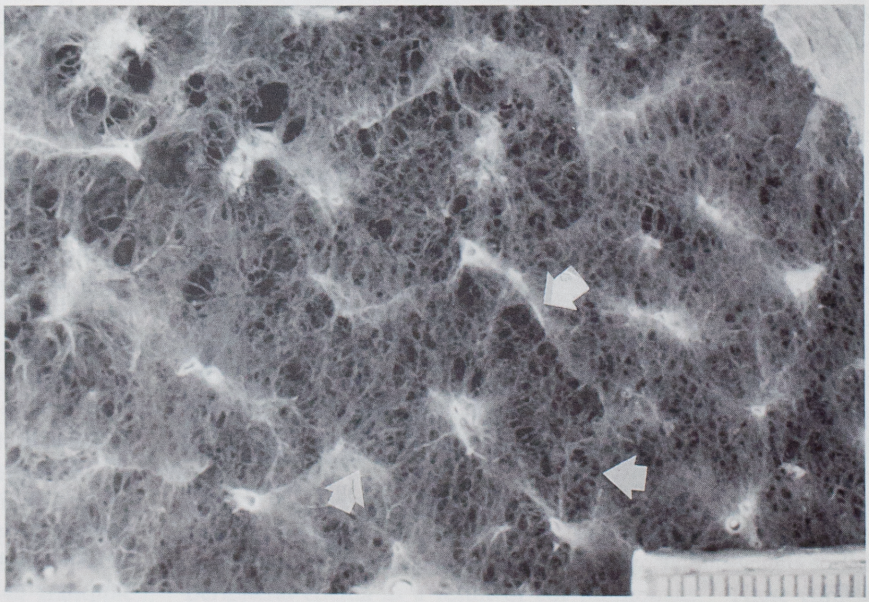

FIGURE 26-6. Gross appearance of panacinar emphysema. Whole lobules (*arrows*) are filled with enlarged air spaces.

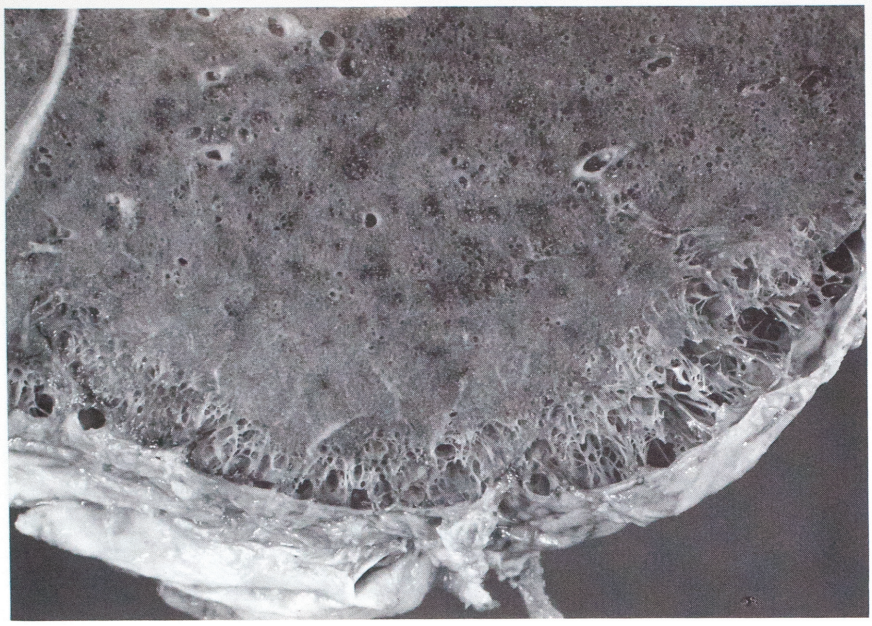

FIGURE 26-7. Irregular emphysema in a subpleural location in an adult patient with pleural fibrosis with adhesions. The remainder of the lung shows a mild degree of centrilobular emphysema. (Contributed by the editor.)

FIGURE 26-8. A coronal slice of the whole right lung shows severe centriacinar emphysema, preferentially involving the upper lung field. However, the individual lesions appear panacinar. This appearance is typical of emphysema in patients dying of chronic obstructive pulmonary disease.

distinction may appear imaginary.[30] Nonetheless, the bulk of evidence is that on the basis of location within the lung, morphology of mild examples, and subtle differences in related airway pathology, a strong argument can be made for considering them separate diseases.[31,32]

Some general advice may simplify the above matter. If the emphysema lesions predominantly involve the upper one half of the lung, they can be regarded as centriacinar. It can be conceived that these lesions started out as typical centriacinar lesions that have grown to fill entire acini. The physician could also use a phrase such as "centriacinar emphysema with panacinar confluence" to designate such lungs. Another piece of helpful advice is to name the predominant type of emphysema by the less severe lesions, which may be easier to characterize. Alternatively, in such lungs with end-stage emphysema, the physician may not wish to attempt to classify the emphysema at all and simply point out its severity and whether it is with or without bullae. Experts have failed to agree in classifying types of emphysema, especially severe degrees;[33] it is more important to use terms that are understood by others and be consistent from case to case.

Designating the severity of emphysema by the percent surface area of lung involved would seem straightforward but has some attendant problems. One problem is that it does not take into account the size of the average emphysema lesion. A lung with 30% emphysema with 1-mm lesions would behave in a manner different from that of a lung with 30% emphysema with 1-cm lesions. Nonetheless, the extent of the emphysema is probably the single most important factor in a diagnosis. Also, although centriacinar emphysema may not involve a large percentage of the lung, the lung parenchyma surrounding the emphysema lesions is probably not being ideally ventilated because the lesions are interposed between the bronchial tree and the normal alveoli. It has been suggested that although the lung tissue in between emphysema lesions may appear normal by routine histology, it is functionally abnormal.

The degree of loss of elastic recoil of the lung in emphysema, which should correlate well with the amount of emphysema, tends to predict more disease than is present, also suggesting that some of the normal tissue is functionally behaving like emphysema.[34]

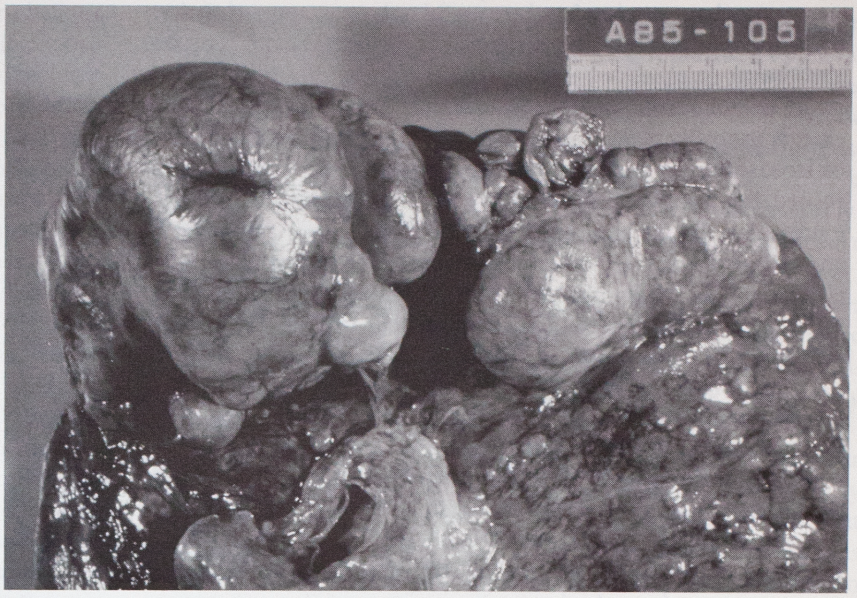

FIGURE 26-9. Gross appearance of subpleural bullae extending into the pleural space.

CLINICAL CORRELATES

Emphysema probably begins to develop in young adults, and with continuing alveolar injury respiratory symptoms appear. However, all evidence for the progression of emphysema is indirect, based on autopsy series at different ages, because the lung cannot be repeatedly examined or imaged accurately enough to follow such changes over time. Specifically, it is not known how individual emphysema lesions behave or whether they achieve their final size shortly after appearance. It is inferred from studies of younger adults compared with older adults that lesions continue to accumulate in smoking individuals. The severity of emphysema necessary to produce symptoms may be as little as 10% lung involvement, and it could be assumed that any patient with 25% involvement would be symptomatic. Yet patients at autopsy may have much more emphysema, even greater than 50%, but no history of respiratory complaints during life. Such correlates are, therefore, only gross approximations.[34a]

Typical symptoms of emphysema (*e.g.*, shortness of breath; dyspnea, especially on exertion; cough) can be seen in other forms of chronic airflow limitation. The common coexistence of chronic bronchitis compounds the difficulty of relating symptoms specifically to emphysema. The separation of symptoms due to small airway disease from those due to emphysema proper is often impossible.

A variety of pulmonary function tests have been advocated to estimate the severity of chronic airflow limitation. The most sophisticated of these give some indication of whether emphysema or airway disease is present.[35,36] However, measurement of lung volumes in emphysema, which typically show a reduced forced vital capacity, increased total lung capacity and residual volume, and decreased maximal breathing capacity, does not correlate well with the extent of anatomic emphysema, or separate it from airway disease.

The reduction of expiratory flow in emphysema, such as the forced expiratory volume in 1 second (FEV_1) or the ratio of FEV_1 to forced vital capacity (FEV_1/FVC), are similarly nonspecific for the diagnosis or estimation of the severity of emphysema. Measurement of diffusing capacity of carbon monoxide, either steady-state or single-breath, correlates best with severity of anatomic emphysema, but even this relationship is not close.[37] Hypoxemia and hypercapnia in arterial blood also lack the sensitivity to predict the severity of anatomic emphysema.

Two major mechanisms are operative in producing slowing of expiratory airflow in emphysema: the concomitant presence of small airway disease, and dynamic collapse of small airways because of loss of alveolar support. The first mechanism—small airway disease—consists of a group of histologic findings, largely chronic inflammation, mural fibrosis, muscular hypertrophy, and mucus plugs, which narrow the airways sufficiently to limit airflow. Like emphysema, the presence of these changes is strongly correlated with cigarette smoking, and smoking is considered causative. Disease of these small airways, which are 2 mm or less in diameter and nonalveolated, is the underlying pathology in those bronchitic patients with airflow limitation, but it occurs in varying degrees in patients who seem clinically to have predominantly emphysema (see Chap. 30).[30]

Dynamic collapse of small airways occurs when structurally normal small airways narrow on expiration because luminal pressures are transiently less than alveolar pressure. Normal alveolar septa are arranged radially around small airways and function as tethers or guy wires, maintaining airway patency and shape. Emphysema lesions, either centriacinar or panacinar, destroy alveoli around airways and reduce the number of alveolar septal attachments, permitting distortion of airway shape, especially because their walls are thin and lack the support of cartilage plates or abundant collagen.[33] Thus, the lesion of emphysema is in the alveolar parenchyma, but the cause of airflow limitation is collapse of small airways (*i.e.*, dysfunction).

In the spectrum of emphysema and airway disease that constitutes COPD, some attention has been given to the extremes, that is, pure emphysema or pure bronchitis. Patients with pure emphysema at autopsy tend to have emphysematous changes on chest films, do not produce much sputum, develop cor pulmonale late or not at all, and do not become hypercapneic. These are known as type A patients or pink puffers, because they typically are barrel-chested and dyspneic. The type B patients or blue bloaters are just the opposite; their names derive from the appearance of cyanosis as a result of ventilation-perfusion mismatch in the lungs and peripheral edema as a result of cor pulmonale.[36] These clinical

stereotypes have persisted and are useful only as an approximation of disease type and severity; patients who fall into just one type are a minority.

Cor pulmonale, or right heart failure due to pulmonary disease, is probably most closely related to the severity and duration of hypoxemia. It is not surprising, then, that cor pulmonale is related, but not closely, to the severity of emphysema.[38–42] It is not unusual to observe at autopsy a patient with severe emphysema and minimal small airway disease who has no hypertrophy of the right ventricle and only modest acute dilatation of this chamber. Thickening of the walls of small muscular arteries does occur frequently in emphysema, probably because of local hypoxia.

The course of patients with symptomatic COPD presumably due to emphysema is a gradual decrease in pulmonary function with increasing symptomatology over years, even decades.[43] A yearly rate of decline in measurements of expiratory flow rates, resting heart rate, and arterial carbon dioxide levels correlates with prognosis.[44] Patients with clinical emphysema have a 10-year mortality rate of 60%.[45] Acute episodes of bronchitis or pneumonia are common and may lead to acute respiratory failure. Common immediate causes of death include acute respiratory infections, pulmonary thromboemboli, myocardial infarcts,[46] and the emphysema itself, with acute cor pulmonale and clinical respiratory failure.

In addition to acute and chronic cor pulmonale, other conditions may be associated with symptomatic emphysema. The cor pulmonale typically produces some degree of hepatic and splenic enlargement as a result of passive hyperemia, as well as peripheral edema. Whether or not the left side of the heart is abnormal in patients with emphysema and cor pulmonale is controversial. Some studies have shown no left heart abnormalities, but others have demonstrated increased fibrosis of the myocardium and hypertrophy of the left ventricle.[45]

Patients treated with corticosteroids develop adrenal cortical atrophy and centripedal fat deposits, especially in the thorax. A chronic corticosteroid-induced myopathy also may develop[46,47] and with high doses may even involve respiratory muscles.[48] Opportunistic infections, typically fungal, have also been described in steroid-treated emphysema.[49] Peptic ulcer is said to occur in more than one fifth of patients with clinical COPD[50] and in some cases may be due to corticosteroid therapy.[51] A curious finding at autopsy in COPD is brown fat transformation in the periadrenal area, a normal finding only in the fetus and newborn; this change appears to reflect the duration and severity of arterial hypoxemia.[51a]

PATHOGENESIS

Two major associations form the basis of the present understanding of cause and pathogenesis of emphysema. These are the development of diffuse panacinar emphysema in patients with genetically decreased blood AAT levels, and the increased frequency of emphysema, particularly centriacinar disease, with cigarette smoking. Both of these findings are linked by the protease-antiprotease hypothesis, which states that emphysema develops from an excess of elastase secretion as a result of inactivation by antiproteases (*i.e.*, antielastases), particularly AAT.

The story of AAT unfolded in the early 1960s in Sweden, as the then-new technique of serum protein electrophoresis was applied to samples from patients with COPD.[52,52a] A few of these patients had virtually no α_1-globulin in their serum, the globulin that had been shown to constitute 90% of AAT. Further studies of relatives, examining the trypsin inhibitory capacity of serum, demonstrated a heterozygous state and uncovered more cases.[53]

Patients with severe AAT deficiency usually presented clinically with emphysema in early adulthood; regular smokers presented earlier than nonsmokers. The emphysema was panacinar, usually basilar in distribution. The autosomal dominant gene for AAT deficiency was common in the Scandinavian population, with nearly 5% heterozygotes and an incidence of severe deficiency of about 1 in 1700 people. This frequency, which is nearly the same as that of cystic fibrosis in Caucasians, is much higher than in the rest of Europe or the United States, suggesting that the gene originated there. Although it was recognized that other serum proteins also functioned as antiproteases, such as β_2-microglobulin and α_1-chymotrypsin, AAT emerged as the single most important serum and tissue antiprotease in man.

More than 75 alleles of the AAT gene have been recognized.[54,55] Nearly all of these have been designated by letters, except for the null allele, in which there is no AAT production at all and no messenger RNA. Because the phenotypic expression of AAT levels depends on each of the two genes inherited, a person's phenotypic expression of AAT has been designated by the abbreviation Pi, for protease inhibitor, followed by the letters or names of the two alleles. The alleles can be grouped into four main categories: normal serum levels and activity of AAT, low serum AAT and activity, complete absence of AAT, and a dysfunctional form of AAT.[56] The alleles that are associated with normal serum AAT include the PiMM phenotypes that constitute about 95% of most populations. In addition to the Z allele, a few other rare variants of the M and the P allele are associated with low serum AAT, lung disease, and sometimes liver disease. Patients with no serum AAT have some type of null allele and have lung but not liver disease. A dysfunctional form of AAT with normal serum levels but no effective antiprotease activity has been described. The most common heterozygotes are PiMZ; despite modestly reduced serum levels of AAT, such people do not seem at increased risk for lung disease.[57]

AAT is an acute-phase reactant synthesized by the liver. Within a few years of the discovery of AAT and emphysema, it was noted that some patients with AAT deficiency developed cirrhosis.[58] With the most common type of severe AAT deficiency, homozygous ZZ, AAT accumulates in rough endoplasmic reticulum of the liver as globules that can be easily visualized with periodic acid-Schiff stains[59] or demonstrated with immunohistochemistry with the use of antibodies to AAT.[60] Apparently, the Z variant molecule has a single amino acid substitution at position 342, with glutamic acid being replaced by lysine.[56] This substitution takes place at the base of a reactive loop of the molecule and allows it to insert into an adjacent molecule rather than the same molecule.[61] Such polymerization causes retention of AAT in the liver and interferes with its antielastase functions. Storage in the liver apparently accounts for the development of liver injury, which eventuates in cirrhosis. Transplantation of the PiZZ gene into mice with normal AAT has been shown to cause AAT accumulation in the liver and liver injury.[62]

Our understanding of the development of emphysema in patients with normal serum levels of AAT is based on several groups of observations. Many studies have shown that the inci-

dence and severity of emphysema are related to the amount of cigarette smoking.[63–66] Young smokers often develop a histologic lesion in respiratory bronchioles called respiratory bronchiolitis, consisting of brown-pigmented macrophages, often with mild inflammation (see Chap. 30).[67] In older smokers, these lesions tend to disappear and be replaced by centriacinar emphysema lesions.[68] Thus, there is good morphologic evidence that cigarette smoke injures respiratory bronchioles, and this injury may result in emphysema.

In 1964, Gross and colleagues instilled proteinases into the lungs of experimental animals and produced emphysemalike lesions.[68a,69] Further studies showed that elastase was the crucial protease, and the disease mimicked human emphysema both anatomically and physiologically. Figure 26-10 shows centriacinar air-space enlargement in a rabbit lung following elastase administration from such a study.[70] It was then theorized that cigarette smoke could, through its irritative effects, promote the release of elastase by resident lung cells, perhaps in excess of the locally available AAT. After considering both neutrophils and macrophages as sources of elastase release following smoking, researchers have implicated release of neutrophil elastase as a key pathogenetic step in the genesis of emphysema.[71] Data from bronchoalveolar lavage support this hypothesis as well, because smokers have a higher total cell count and an increased percent of neutrophils (*i.e.*, less than 1% in nonsmokers *versus* 2% to 3% in smokers).[72] Functional elastase can also be found in lung fluids from smokers. Additional studies have shown that cigarette smoke itself tends to neutralize AAT by oxidizing methionine near the active site of the AAT molecule.[56]

All of this evidence can be assembled into the protease-antiprotease hypothesis of the pathogenesis of emphysema. Of the several antiproteases in the human body, including α_1-antichymotrypsin and α_2-macroglobulin, AAT has been found to be the most important.[73] Patients with low or absent serum and tissue levels of AAT, as seen with the PiZZ or Pi_{null} phenotypes of AAT deficiency, develop emphysema because the constant release of neutrophil elastase in lung in response to any noxious stimulus is not neutralized by AAT. Elastase causes the chronic, smoldering tissue destruction and remodeling recognized as emphysema, in this case, panacinar, because the whole lung is perfused by blood low in AAT. In smokers with normal AAT, cigarette smoke causes recruitment of neutrophils to the acinus and increased elastase secretion, especially in the proximal acinar area. Despite the presence of AAT, the balance between protease and antiprotease is tilted slightly in favor of the former, and elastase produces emphysema in the centriacinar region at an insidious but progressive pace.

It has been reported that young intravenous Ritalin abusers develop severe emphysema.[74a] It has been hypothesized that the intravenous particulates injected, chiefly talc, may produce sufficient tissue injury to release elastases that are not adequately neutralized by AAT.

Cigarette smoke also directly neutralizes some AAT and thus reduces the effective concentrations in lung tissue. New data may modify or clarify some aspects of this pathogenetic sequence, but this hypothesis accounts for the major observations in the genesis of emphysema. A final emerging observation is the association between childhood respiratory illnesses and adult COPD.[74] It could be speculated that such infections in childhood could interfere with lung growth in such a way that the effects of cigarette smoke would be potentiated. Clearly, host factors are important, because most cigarette smokers do not develop COPD, and not even all patients with PiZZ AAT deficiency succumb to emphysema.

EPIDEMIOLOGY

COPD embracing both emphysema and airway disease with airflow limitation is one of the major causes of death in the United States.[75] However, approaches to the incidence of emphysema in a living population are hampered by its similarities clinically and physiologically to other forms of chronic airflow limitation. Because the definition of emphysema is essentially morphologic, autopsy lungs have been used to determine the incidence and severity of emphysema in various populations. With the advent of thin-section computed tomography as an accurate means of quan-

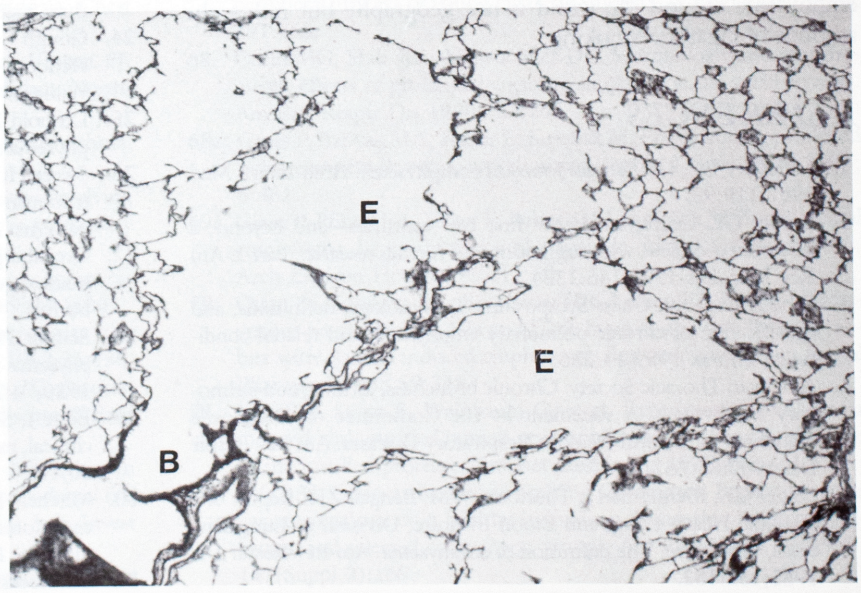

FIGURE 26-10. Histology of experimental emphysema in the rabbit. The lesions (E) are in the proximal acinus, similar to centriacinar emphysema, as recognized by the lesions' relations to the terminal bronchiole (B). (H & E stain; low magnification.)

titating emphysema,[76,77] the incidence of this disease in a living population may soon be realized.

A review of autopsy morphologic studies addressing the question of the incidence and severity of emphysema in various populations and countries shows remarkable similarities in disparate populations.[78] The majority of such epidemiologic studies have looked at both men and women with an average age of 60 years or older. For the industrialized areas of Europe, North America, and Japan, some emphysema was found in approximately one half to two thirds of this population. However, studies from regions that are less industrialized (*e.g.*, Bombay, India; Papua, New Guinea; Uganda) have demonstrated emphysema in 25% to 50% of lungs at autopsy, and a study from Jamaica found a 90% incidence of emphysema in a series of cases.[79] Factors such as cigarette smoking for the Jamaican population and cooking over fires in huts with poor ventilation in the New Guinea population are probably etiologic factors leading to emphysema. As expected, most of the cases of emphysema are mild; lesser degrees of moderate emphysema constituted approximately 25% of all the emphysema seen, and a small amount of severe emphysema is present in approximately 10% of cases. Emphysema predominates in males compared with females in a ratio of about 2–3 : 1, although in some populations it ranges as high as 8 : 1 to 10 : 1.[78] With increasing cigarette use by women over the last decade, it would be expected that this proportion would edge closer to equal percentages of emphysema in both genders.

Methodologic differences in selecting lungs at autopsy and grading the type and severity of emphysema make it difficult to draw any definitive conclusions from these studies. Nonetheless, it is evident that emphysema is a common finding in older adults at autopsy, and it is seen in men more than in women. Mild degrees of emphysema are most common and severe emphysema is least common. Most emphysema is centriacinar in type, which probably reflects cigarette smoking in the population. Because only a small percentage of emphysema is linked to Pi abnormal phenotypes, the variable distribution of these phenotypes in different ethnic groups probably does not play an important part in the differences in the incidence and severity of emphysema around the world. Taken as a whole, these epidemiologic studies suggest that by far the most important factor in the incidence and severity of emphysema around the world is not geography but rather the amount of cigarette smoking.

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