TABLE 1.—Comparison of mucus gland size in smokers and nonsmokers

Assessment of mucus gland enlargement	Author	Findings in smoking category			
		Non-smokers	Smokers	Light and moderate smokers	Heavy smokers
Reid index	Reid (1960)			0.46	0.43
	Thurlbeck et al. (1963)	0.43	0.50	0.45	0.53
	Thurlbeck and Angus (1964)	0.44	0.49		
	Bath and Yates (1968)	0.45	0.49		
	Hayes (1969)	0.32	0.33		
	Scott (1973)	0.41	0.46		
Mucus gland proportion	Ryder et al. (1971) (men)	14.5%	17.8%		
	Ryder et al. (1971) (women)	14.5%	17.1%		
	Sobonya and Kleinerman (1972)	11.2%	10.7%		
	Scott (1973)	14.1%	14.4%		
	Cosio et al. (1980)		Increased		
	Pratt et al. (1980)	9.3%	12.6%		
Frequency of cases with MGH[1] expressed as a percentage of cases in the group	Field et al. (1966) (men)	12%	37%		
	Field et al. (1966) (women)	18%	26%		
	Megahed et al. (1967)	14%	61%		
	Petty et al. (1967)	8.8%	37%		
	Vargha (1969)	18%	44%		

[1] MGH = Mucus gland hypertrophy.

inflammation and edema of the wall (Reid 1954), increase in bronchial smooth muscle (Hossain and Heard 1970; Takizawa and Thurlbeck 1971), and diminished cartilage, which is related more to emphysema than to chronic bronchitis (Thurlbeck et al. 1974a).

Peripheral (Small) Airways

General Review

As indicated, it was as recent as 1968 that the obstruction in patients with chronic airflow obstruction was conclusively shown to be due mainly to lesions in airways less than 2 or 3 mm in diameter. However, abnormalities in these airways had long been recognized. Indeed, Laennec (1962) pointed out in 1826 that air remained trapped in emphysematous lungs even when the major bronchi had been opened, and he reasoned that the source of the air-trapping was obstruction in the airways peripheral to the opened ones. Since then, numerous descriptions have been made of the peripheral airways in severe chronic airflow obstruction (see Table 2). Smokers were not compared with nonsmokers in any of these series. The probable reason is that for a long time it was thought that bronchiolitis was an infective complication of chronic bronchitis. Only very recently, and from studies in patients with mild chronic airflow obstruction,

has the link between smoking and peripheral airway lesions become established.

Hogg et al. (1968) not only found that the peripheral airways were the site of airflow obstruction in patients with severe disease, but also observed that peripheral airways contributed only about 15 percent of resistance to flow in normal lungs. It followed that considerable disease could be present in these peripheral airways without airway resistance being measurably increased. It was reasoned also that standard tests of expiratory function, such as the FEV_1 and the FEF_{25-75}, might not be abnormal in the presence of significant disease. Thus a variety of "tests of small airway function" were devised; these evolved to the single breath nitrogen washout test and to flow volume studies, in some instances comparing the effect of breathing helium mixtures with the effect of breathing room air. It soon became apparent that these tests could be abnormal when the FEV_1 was greater than the 80 percent predicted and that tests of small airway function could return to normal after cessation of smoking (Buist et al. 1976, 1979; Beck et al. 1981; Bouse et al. 1981). The term "small airways disease" was and is often applied to these abnormalities. It then became of interest to determine what the lesions in the airways were. Long before this, Reid (1955) had studied nine lungs resected from patients with chronic bronchitis and two lungs from chronic bronchitics obtained at autopsy. She found excess intraluminal mucus and narrowing and obliteration of airways, as assessed subjectively. Because the surgical patients also had lung cancer, most likely they were chronic smokers. Matsuba and Thurlbeck (1973) compared the airways of chronic bronchitics to those of nonbronchitics in nonemphysematous lungs. All the bronchitics were smokers and two nonbronchitics were smokers. Morphometrically, they found obvious narrowing of airways less than 2 mm in diameter, which also contained excess mucus.

The important study by Cosio et al. (1978), using surgically resected lungs, showed for the first time that abnormal tests of small airway function were related to abnormal morphology. There were 34 smokers and 2 nonsmokers in their group. A variety of abnormalities were observed, including inflammation, squamous cell metaplasia, ulceration, fibrosis, pigmentation, and increased muscle. They developed a score that summed the observed lesions (the total pathology score), and divided their patients into four groups on the basis of this score. They showed that as the total pathology score increased, tests of small airway function (single breath nitrogen test and flows on air and helium mixtures) deteriorated, as did standard tests of pulmonary function such as the FEV_1 and FEF_{25-75}. The data concerning smoking are hard to interpret, but the smoking index (number of cigarettes smoked per day times number of years smoked) increased from groups I to III and was similar in groups III

TABLE 2.—Occurrence of lesions of peripheral airways in patients with severe chronic airflow obstruction

Authors	Disease investigated	Abnormalities found
Laennec (1962)	Emphysema	Obstruction to flow in peripheral airways
Spain and Kaufman (1953)	Emphysema	Mural inflammation and fibrosis of bronchioles
Reid (1954)	Chronic bronchitis	Bronchiolitis, bronchiolar obliteration, and mucus plugging
Leopold and Gough (1957)	Centrilobular emphysema	Inflammation, fibrosis with narrowing of 60% of bronchioles supplying centrilobular space
McLean (1958)	Emphysema	Inflammation of proximal respiratory bronchioles, mucus plugging, and loss of bronchioles
Anderson and Foraker (1962)	Emphysema	Collapse of bronchioles due to loss of alveolar attachments
Pratt et al. (1965)	Centrilobular emphysema	Loss or distortion of the radial support of bronchioles
Anderson and Foraker (1967)	Emphysema	Loss of bronchioles in patients under age 70
Hogg et al. (1968)	Emphysema with severe chronic airflow obstruction	Inflammation and fibrosis of bronchi and bronchioles and mucus plugging
Mitchell et al. (1968)	Chronic airflow obstruction and severe emphysema	Inflammation, atrophy, goblet cell metaplasia, squamous metaplasia, and mucus plugs in bronchioles
Bignon et al. (1969, 1970)	Cor pulmonale and centrilobular emphysema	Inflammatory narrowing and fibrosis, loss of bronchioles, and mucus plugging
Karpick et al. (1970)	Respiratory failure	Goblet cell metaplasia
Linhartova et al. (1971)	Emphysema	Plugging of bronchioles with inflammatory cells and mucus
Matsuba and Thurlbeck (1972)	Severe emphysema and chronic airflow limitation	Loss of lumen of airways less than 2 mm in diameter due primarily to narrowing and mucus plugs
Linhartova et al. (1973, 1974, 1977)	Emphysema	Distortion, tortuosity, and irregular narrowing of bronchioles
Scott and Steiner (1975)	Cor pulmonale	Lack of filling bronchioles of less than 1 mm
Scott (1976)	Chronic airflow obstruction	Loss of airway lumen
Mitchell et al. (1976)	Chronic airflow obstruction obstruction	Chronic inflammation ($r=0.48$), narrowing (0.29), fibrosis (0.27), goblet cell metaplasia (0.24), and fewer small airways (–0.18)

and IV. The lesions that were different in group II from lesions in group I were squamous cell metaplasia, inflammation, and fibrosis. Fibrosis and squamous cell metaplasia increased steadily from groups I to III. Increased muscle and goblet cell metaplasia occurred only in group IV. One extrapolation of these data is that inflammation in the peripheral airways is the initial event produced in response to cigarette smoke. This inflammation leads to, or is associated with, squamous metaplasia and mural fibrosis. Goblet cell metaplasia and increase in muscle subsequently occur and are associated with decrements of function.

Berend et al. (1979) did a similar study on 21 smokers and 1 nonsmoker, and added the important information that airway narrowing occurred and was associated with abnormalities of the single breath nitrogen washout test and the FEF_{25-75}. The data were reanalyzed subsequently (Berend et al. 1981b) and showed that inflammation was the lesion associated with the most abnormalities in tests of expiratory function. Airway inflammation was significantly related to abnormalities of the FEV_1, FEF_{25-75}, slope of phase III of the single breath nitrogen test, and closing volume expressed as a percentage of vital capacity. The authors also noted that as the total pathology score got worse, the airways diminished in caliber in surgically derived lungs, but not in autopsy lungs. They noted that airway caliber was larger in autopsy lungs than surgical lungs, and suggested that this represented functional narrowing due to increased muscle tone, which was caused by release of mediators affecting the muscle directly or reflexly.

Studies of lungs at autopsy have shown correlations between airway lesions and abnormal tests of function. Petty et al. (1980, 1982) have shown that correlations exist between inflammation, and increased muscle and elevations in the closing capacity; that occlusion of airways by cells and mucus, inflammation, and increased airway muscle are related to abnormalities of the slope of phase III of the nitrogen washout; that airway narrowing is closely related to the FEV_1, FEF_{25-75}, and slightly less well related to closing capacity. Similarly, Berend et al. (1981a) showed an association between post-mortem closing capacity and both peripheral airways inflammation and a total pathology score. Decrease in maximum flow at a transpulmonary pressure of 5 cm H_2O was related to inflammation and the total pathology score, but not as well related to airway narrowing (Berend and Thurlbeck 1982). Morphologic abnormalities similar to those found in autopsy lungs have been found in surgically excised lungs derived almost entirely from smokers, and these in turn have been related to abnormal tests of small airway function.

Smoking and Lesions of Peripheral (Small) Airways

An increase in goblet cells was the first abnormality of peripheral airways noted in smokers. The observation was made in bituminous coal workers. In nonsmokers, about 0.66 percent of peripheral airway cells were found to be goblet cells; in smokers, this rose to about 1.0 percent (Naeye et al 1971).

The critical observation, both factually and conceptually, was that of Niewoehner et al. (1974). In an autopsy study of men under the age of 40 who died suddenly elsewhere than in the hospital, they compared lesions of bronchioles and respiratory bronchioles (airways with both nonrespiratory epithelium and alveoli in their walls) in smokers and nonsmokers. Emphysematous lungs were excluded, and the smoking history was obtained by personal interview with close relatives, using a standard questionnaire. The researchers found that intraluminal mucus, mural edema, peribronchiolar pigment, peribronchiolar fibrosis, denuded epithelium, mural inflammatory cells, and respiratory bronchiolitis were more severe in the smokers. The last three were significantly different statistically. They emphasized the importance of respiratory bronchiolitis, which consisted of aggregates of brown macrophages in and around the first and second order respiratory bronchioles and was associated with edema, fibrosis, and epithelial hyperplasia in adjacent bronchioles and alveolar walls. Bronchiolitis was found in all of the smokers, but in only 5 of the 20 nonsmokers, and it was the lesion that showed the greatest difference between smokers and nonsmokers. Since respiratory bronchiolitis was found in precisely the same regions where centrilobular emphysema is found in subjects 20 years older, the researchers suggested that this lesion might evolve into emphysema. This observation fits well the proteolytic–antiproteolytic hypothesis of the pathogenesis of emphysema.

Ebert and Terracio (1975) compared the peripheral airways in resected lungs of 22 smokers and 3 nonsmokers and found that the number of Clara cells (the tall nonciliated airway cells thought to be secretory, although the nature of their secretion is not completely certain) was diminished, as assessed subjectively, and the number of goblet cells was increased, as assessed quantitatively.

Two laboratories have concentrated on the association between smoking and lesions of vessels as well as of airways. One has used autopsy-derived lungs (Cosio et al. 1980; Hale et al 1980); the other, surgically excised lungs (Wright et al. 1983a, b, in press). The first material has the advantage that the entire lung can be examined, but has the disadvantage that agonal changes may affect the airway; the second has the advantage that agonal changes are absent and structure–functional studies can be done, but has the serious disadvantage that usually only a part of the lung is examined. Because of the wide variation in severity of emphysema from lobe to

lobe, emphysema in the whole lung cannot be assessed from a single lobe. Also, airway inflammation may not be evenly distributed through the airways (Berend 1981; Hale et al. 1980).

Cosio et al. (1980) studied 14 nonsmokers with an average age of 71.6 years and 25 long-term smokers with an average age of 58.4 years. The total pathology score was significantly higher in the smokers; in them, but not in the nonsmokers, the total pathology score was significantly related to age. Respiratory bronchiolitis was more common in the smokers, and of the components of the total pathology score, goblet cell metaplasia ($p < 0.001$), inflammation of the bronchiolar wall ($p < 0.01$), and smooth muscle hypertrophy ($p < 0.05$) were significantly more abnormal in the smokers. Smokers had an excess of airways less than 400 μ in diameter, also related to the total pathology score. Because goblet cell metaplasia and increased smooth muscle were not significantly increased in the researchers' previous study of young smokers (Niewoehner et al., 1974), they concluded that these lesions were a late complication of cigarette smoking. They noted that there was a considerable similarity of all lesions of both smokers and nonsmokers, and felt that this indicated the existence of other causes of small airway lesions. They also made the interesting suggestion that the relationship between the total pathology score and the proportion of airways less than 400 μ in diameter might indicate a predisposition of subjects with small airways to develop peripheral airway lesions.

Wright et al. (1983b) studied 9 nonsmokers, 51 current smokers, 18 ex-smokers who had quit less than 2 years, and 19 ex-smokers who had quit more than 2 years. The only lesion of the bronchioles that distinguished the nonsmokers from the smokers and the long-term ex-smokers was goblet cell metaplasia, although there were obvious differences in pulmonary function among these groups. The significance of goblet cell metaplasia may be related to mucus production in airways not usually lined by mucus. There is evidence that they are lined by surfactant. If this is displaced by mucus with a higher surface tension it will produce narrowing difficult to detect by standard morphological methods. Respiratory bronchiolitis was more severe in the smokers and ex-smokers than in the nonsmokers. No differences were noted between the ex-smokers and smokers. This study has recently been extended (Wright et al., in press), and correlations between both bronchiolar inflammation and respiratory bronchiolitis and the FEV_1 were evident. When the FEV_1 was greater than the 80 percent predicted, the most important determinant of abnormalities of tests of small airway function was respiratory bronchiolitis. Thus, respiratory bronchiolitis may not only represent a stage in the pathogenesis of centrilobular emphysema, but also result in abnormalities of the single breath nitrogen test and other tests of small airway function.

It is not certain why cessation of smoking results in improvement of lung function. The most likely reversible parameter is inflammation; the lack of difference between nonsmokers and the other groups in the study by Wright et al. (1983b) is very surprising in view of the observations of Niewohner et al. (1974) and Cosio et al. (1980), but may be due to the very small number of nonsmokers studied and the fact that the nonsmokers had lung lesions for which resection was performed. An additional factor is the use of lobes in the study, which in the small group of normals may produce distortions in the data because of lobar variations in the total pathology score.

Vascular Lesions Related to Smoking

At first sight it may appear surprising that vascular lesions are detectable in asymptomatic smokers or those with only mild or moderate chronic airflow obstruction. On reflection, this could be anticipated. Severe chronic airflow obstruction, usually related to smoking, is often accompanied by pulmonary artery hypertension; mild chronic airflow obstruction might be associated with mild pulmonary artery hypertension and vascular lesions. The first study (Hale et al. 1980) involved the same cases reported by Cosio et al. (1980). They found that the smokers had an increased number of arteries less than 200 μ in diameter and also an increased medial and intimal thickness of the pulmonary arteries. The intimal thickness was increased more in those vessels of less than 200 μ in diameter. Both intimal and medial thickness were directly related to the total pathology score. Wright et al. (1983a) found an increase in the vessel area from an average of 0.12 mm^2 in nonsmokers to approximately 0.3 mm^2 in smokers. Intimal area expressed as a proportion of vessel area increased; there was an absolute increase of the medial area, but no proportional change. The adventitial area also increased in absolute terms, but the adventitial proportional area was decreased and was related to the pulmonary wedge pressure. Pulmonary artery pressures were normal at rest, but abnormal and reversible by oxygen on exercise in the smokers with the worst airway inflammation and emphysema.

Emphysema

Of the lesions associated with chronic airflow obstruction, emphysema has been the one most clearly associated with tobacco smoking. There are several different types of emphysema, however, and cigarette smoking has not been clearly linked to, or examined in, all forms of the disorder. Therefore, the definition and classification of emphysema are reviewed before discussing the association between smoking and emphysema.

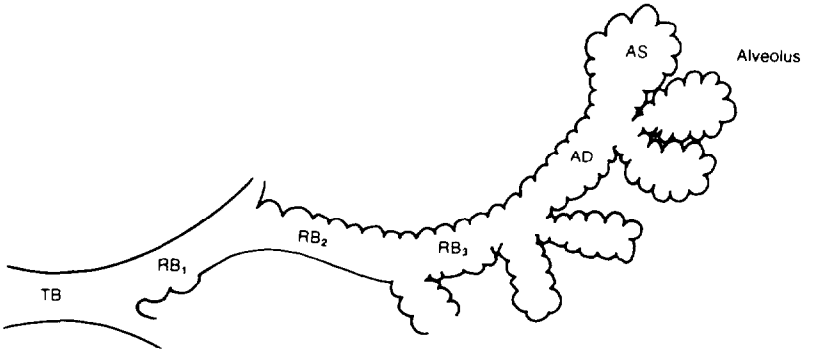

FIGURE 1.—Components of the acinus

NOTE: TB: terminal bronchiole; RB_1, RB_2, RB_3: the three orders of respiratory bronchioles; AD: alveolar duct; AS: alveolar sac.

SOURCE: Thurlbeck (1976).

Definition

Emphysema is defined as an abnormal enlargement of the air spaces of the lung accompanied by destruction of alveolar walls (World Health Organization 1961; American Thoracic Society 1962). Thus, emphysema is a disorder of anatomy, and one must know the appropriate normal anatomy in order to understand the pathology of emphysema. The structure involved is the acinus, the unit gas-exchanging structure of that part of the lung containing alveoli. The last purely conducting airway is the terminal bronchiole; structures distal to it constitute the acinus. The acinus is a complex unit, but a simplified model will suffice (Figure 1). The structures immediately before the terminal bronchiole are the respiratory bronchioles, which, as indicated previously, have both alveoli and nonalveolated epithelium forming their walls; thus, respiratory bronchioles both conduct and exchange gas. Proceeding distally, progressively more alveoli appear in the walls of respiratory bronchioles, of which there are three orders in the usual model of the acinus. Alveolar ducts succeed respiratory bronchioles, and their walls are entirely alveolated. Alveolar ducts lead into alveolar sacs, the terminal respiratory structures, which are likewise completely alveolated.

Classification

Emphysema is classified by the way it involves the acinus, and four forms of emphysema are usually recognized (Thurlbeck 1976): (1) proximal acinar emphysema, (2) panacinar (panlobular) emphyse-

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ma, (3) distal (paraseptal) acinar emphysema, and (4) irregular emphysema.

Proximal Acinar Emphysema

In *proximal acinar emphysema,* the respiratory bronchioles are selectively or dominantly involved. Emphysema involving the proximal part of the acinus is found in two different circumstances—centrilobular emphysema and focal emphysema.

Proximal acinar emphysema is the common form of nonindustrial emphysema and is associated with inflammation of the distal airways (Leopold and Gough 1957) and of the walls of emphysematous spaces. This form of emphysema is usually referred to as centrilobular emphysema (Figure 2) because the lesions lie close to the center of the secondary lobules. The emphysematous spaces are found more frequently in the upper zones of the lungs, and centrilobular emphysema is usually more severe there (Thurlbeck 1963a). Involvement of the lung is characteristically quite uneven; some respiratory bronchioles are spared or slightly involved, whereas others close by may be severely affected, producing large emphysematous spaces. Centrilobular emphysema is frequently associated with chronic bronchitis, and is the form of emphysema most commonly encountered in patients with symptomatic chronic airflow obstruction.

Focal emphysema, or simple pneumoconiosis of coalworkers, also involves the proximal part of the acinus. It can be distinguished from centrilobular emphysema in that there is always a heavy deposit of coal around the emphysematous spaces, the enlargement of respiratory bronchioles is usually moderate, and the process is more uniform through the lung. Simple pneumoconiosis is usually associated with only mild impairment of function, producing only minor abnormalities of gas exchange (Morgan and Seaton 1975).

Panacinar (Panlobular) Emphysema

In *panacinar* or *panlobular emphysema,* there is more or less uniform involvement of the acinus (Figure 3). Controversy exists concerning the distinction between centrilobular and panacinar emphysema; some believe them to be different conditions (Anderson and Foraker 1973), but others believe them to have the same clinical and functional associations (Mitchell et al. 1970). The reason for this disagreement is discussed below. Four different associations of panacinar emphysema are described (Thurlbeck 1976), each with its specific clinicopathologic associations. This view is not shared by all, however.

The classical association of panacinar emphysema is with α_1-antitrypsin deficiency (Eriksson 1965), most commonly with the PiZ

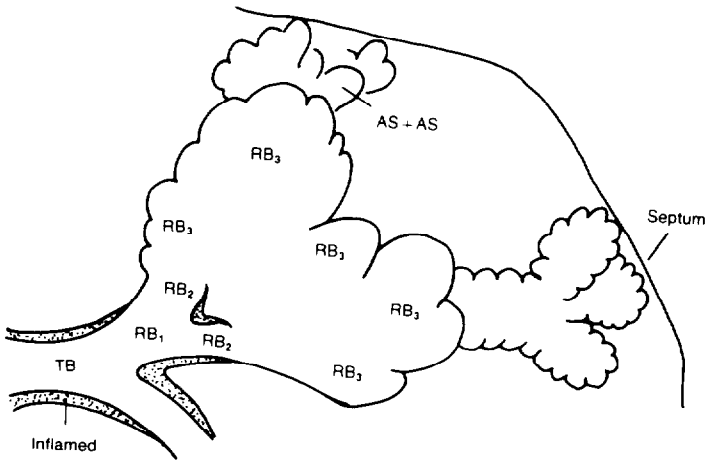

FIGURE 2.—Centrilobular emphysema
NOTE: See footnote to Figure 1 for definitions.
SOURCE: Thurlbeck (1976).

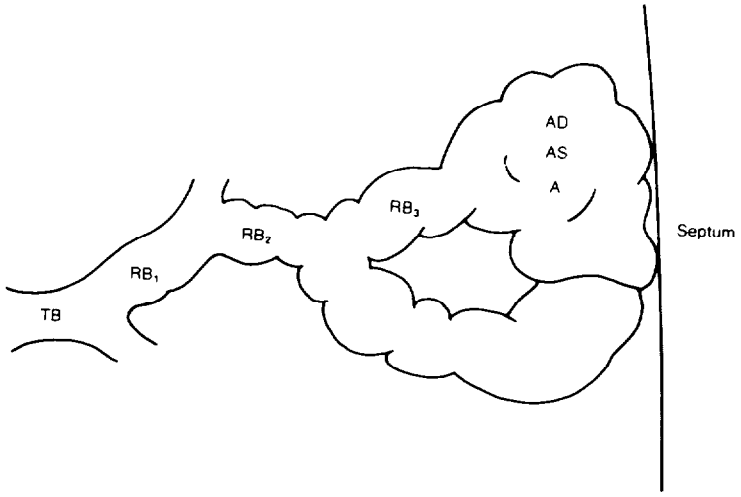

FIGURE 3.—Panlobular emphysema
NOTE: See footnote to Figure 1 for definitions.
SOURCE: Thurlbeck (1976).

phenotype. It is probable that other forms of Pi-associated emphysema, such as PiSZ, are also panacinar in type. Familial emphysema unassociated with α_1-antiprotease deficiency has been shown to be panacinar (Martelli et al. 1974). Familial emphysema is characteristically worse in the lower zones of the lung. Severe, pure panacinar emphysema is uncommon.

Localized panacinar emphysema is found fairly frequently at autopsy (Thurlbeck 1963a). It is found more commonly in older people and is usually not associated with clinical evidence of chronic airflow obstruction. Under these circumstances, it is more frequent in the lower and anterior parts of the lung. It may represent a focal exaggeration of the aging process in the lung, which includes a well documented set of changes (Thurlbeck 1976), including changes in the shape of the lung with an increase in anteroposterior diameter, loss of volume density of alveolar walls, increase in the distance between alveolar walls, decrease of alveolar surface area, increase in volume density of alveolar ducts, and decrease of volume density of alveoli. The reason for referring to these changes with age as the "aging lung" rather than "senile emphysema" is that it is a normal change, affecting virtually all people. The definition of emphysema requires that the enlargment and destruction of respiratory tissue be abnormal; therefore, it is probably inappropriate to categorize these changes as emphysema.

Bronchial and bronchiolar obliteration may be associated with panacinar emphysema. Most commonly it is associated with Swyer-James (1953) or MacLeod's (1954) syndrome of unilateral pulmonary hyperlucency, in which one lung or a major portion of the lung is unduly transradiant. The involved region or regions of the lung characteristically trap air on expiration so that the mediastinum then moves to the unaffected side. The syndrome is usually due to severe acute bronchitis and bronchiolitis in childhood, resulting in obliteration of airways. A detailed study of the lung parenchyma in cases of unilateral pulmonary transradiancy has never been reported, but it seems likely that emphysema may not be present in the affected lung tissue. However, when emphysema is present, it is panacinar in type.

Panacinar emphysema may be found in the lower zones of the lung in patients with upper zonal centrilobular emphysema. The combination of the two forms of emphysema is probably the classical finding in patients with severe chronic airflow obstruction, and it is also one reason for the controversy concerning similarities or differences between centrilobular and panacinar emphysema. Transitions, real or imagined, may be apparent between the upper zonal centrilobular emphysematous spaces and lower zonal panacinar emphysema in this situation. Some believe the transitions are real, and maintain that centrilobular emphysema has progressed to

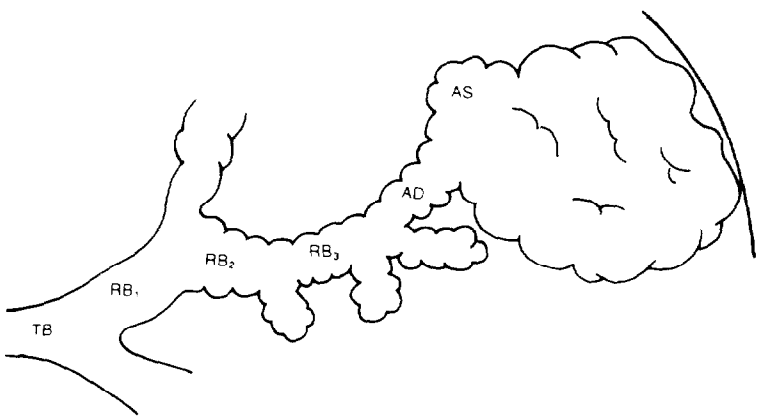

FIGURE 4.—Distal or paraseptal acinar emphysema
NOTE: See footnote to Figure 1 for definitions.
SOURCE: Thurlbeck (1976).

panacinar emphysema and that these lungs should be classified as examples of centrilobular emphysema. Others feel that it is panacinar emphysema, and thus the same lung may be classified differently.

Distal (Paraseptal) Acinar Emphysema

Distal (paraseptal) acinar emphysema is the third generally recognized form of emphysema. In this form, the alveolar ducts and sacs are predominantly involved, and there may be substantial associated fibrosis (Figure 4). Since the distal acinus abuts on pleura, vessels, airways, and lobular septa, the emphysema is worse in these regions. The occurrence of distal acinar emphysema along the lobular septa had led to the term "paraseptal emphysema." A characteristic clinical association of distal acinar emphysema is spontaneous pneumothorax of young adults (Edge et al. 1966).

rregular Emphysema

In *irregular emphysema,* the acinus is irregularly enlarged (Figure 5). It is nearly always associated with scarring. It may be the most ommon form of emphysema, because nearly all lungs on close xamination will disclose a scar associated with emphysema. The najority of these examples of irregular emphysema are unassociated vith symptoms.

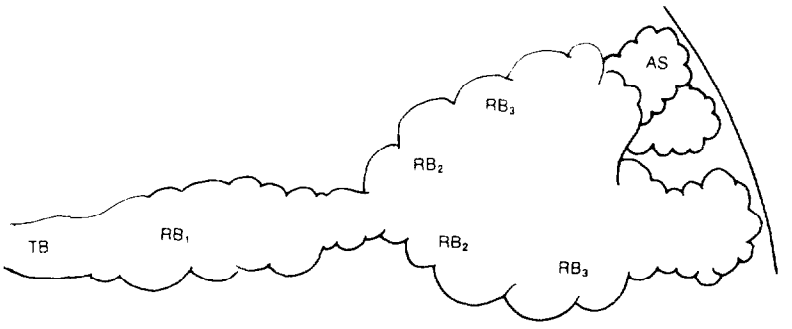

FIGURE 5.—Irregular emphysema
NOTE. See footnote to Figure 1 for definitions.
SOURCE: Thurlbeck (1976).

Tobacco Smoking and Emphysema

The apparently neat and orderly classification described above and the classical examples of emphysema illustrated in original articles and monographs should not obscure the lack of agreement between expert observers in the classification of severely emphysematous lungs (Thurlbeck et al. 1968, Mitchell et al. 1970). Severe emphysema is usually atypical in morphology, and often more than one type of emphysema is present. It might be more rational to speak of "end stage emphysema" when describing an extensively damaged lung, rather than attempting to fit all of the damage under one classification.

These differences in classification may lead to differing assessments of degrees of association between smoking and individual forms of emphysema. For example, Anderson and Foraker (1973) found that all of their 21 patients with centrilobular emphysema were cigarette smokers, whereas 8 of the 17 patients with panacinar emphysema were cigarette smokers. Contrarily, Mitchell et al. (1970) found that 20 of their 21 patients with centrilobular emphysema were cigarette smokers and all 6 of their patients with panacinar emphysema were cigarette smokers.

Including all of the different abnormalities described above under the single term "emphysema" may lead to confusion about the relationship between smoking and emphysema. Each of the different forms of emphysema may have different etiologies; while cigarette smoking is clearly implicated in the etiology of centrilobular emphysema (Mitchell et al. 1970, Anderson and Foraker 1973), it may not play a role in irregular or distal acinar emphysema and is

clearly not implicated in the etiology of unilateral pulmonary transradiancy.

Another problem is the sensitivity with which emphysema is recognized. Thurlbeck (1976) reviewed the incidence of emphysema found at autopsy in 28 series. An extremely wide variation has been recorded, including three series with an incidence of 100 percent. The variation in incidence probably represents the care with which the lung is examined and the threshold for defining emphysema being present as much as a true difference in incidence.

It is not relevant to the present discussion whether rare or unusual disease processes can cause abnormal enlargement of the air spaces or whether, after careful and exhaustive search, all lungs demonstrate minute areas of focal enlargement. The lung has substantial ventilatory reserve; therefore, what is significant is not the presence or absence of any emphysema, but rather the extent or severity of the emphysematous change in the lung. What is both clear and relevant to the present discussion is that the relationship between smoking and emphysema represents an association between smoking and the severity of emphysema, and that the relationship is between smoking and those forms of emphysema commonly found in patients with COLD.

In 1963, clinicopathologic findings (Thurlbeck 1963b) in a group of patients dying at the Massachusetts General Hospital showed that 18 of 38 patients without emphysema were cigarette smokers, whereas all of the 19 patients with severe emphysema were cigarette smokers. A formal study of the relationship between emphysema and smoking was first made by Anderson et al. (1964), who showed that one-third of patients without emphysema, 19 of 37 patients with mild emphysema, 19 of 23 patients with moderate emphysema, and all 6 patients with severe emphysema were smokers. In 1966, an extended study (Anderson et al. 1966) found in the four groups, respectively, that 12 of 33 patients, 58 of 84 patients, 30 of 33 patients, and 14 of 15 patients were smokers. Mitchell et al. (1964) found 62 smokers among 85 patients with no or mild emphysema and 39 smokers among 40 patients with moderate or severe emphysema. These researchers also extended their series (Petty et al. 1967) and found 6 nonsmokers among 57 patients with moderate emphysema and 1 nonsmoker among 61 patients with severe emphysema. A very dramatic difference was shown between smokers and nonsmokers by Ryder et al. (1971). Figures 6 and 7 indicate very graphically the rarity of emphysema of even moderate severity in nonsmokers and the high incidence of emphysema in smokers over 50 years of age. Of the 21 patients in their series whose lungs had a more than 25 percent involvement by emphysema, only 1 was a nonsmoker.

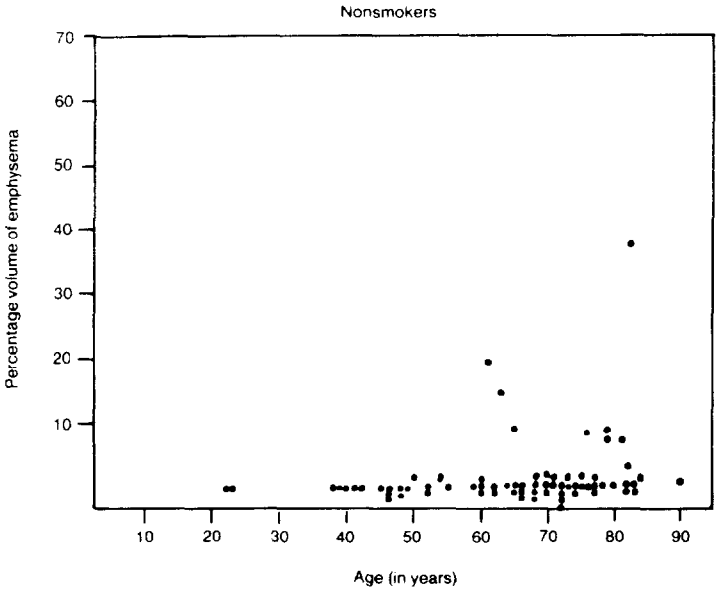

FIGURE 6.—Percentage of lung occupied by emphysema in nonsmokers

SOURCE: Ryder et al. (1971).

Only a small effect of smoking was noted in coal miners by Naeye et al. (1971), an increase from 24.3 percent of the lung involved in nonsmokers to 30 percent in smokers. A much greater effect of smoking was noted by Auerbach et al. (1972), who studied lungs from 2,613 autopsies and were able to obtain smoking histories in 1,831 of the patients. They found that 10 percent of male patients who had not smoked had emphysema; this percentage rose to 53.5 percent for pipe smokers and cigar smokers, 86.9 percent for smokers of less than a pack per day, and 99.7 percent for smokers of more than a pack per day. Of the 130 patients with severe emphysema, 126 smoked more than a pack a day, 2 smoked less than a pack, 2 were pipe or cigar smokers, and none were nonsmokers. Their findings were subsequently extended and confirmed by histologic examination of these lungs (Auerbach et al. 1974). Findings in women were similar. Spain et al. (1973) studied lungs from 134 persons who died suddenly and unexpectedly and who had no previous known pulmonary disease. In men, they found an incidence of emphysema of more than grade 20 (mild emphysema) of 10 percent in nonsmokers, 36 percent in smokers of less than a pack per day, and 39 percent

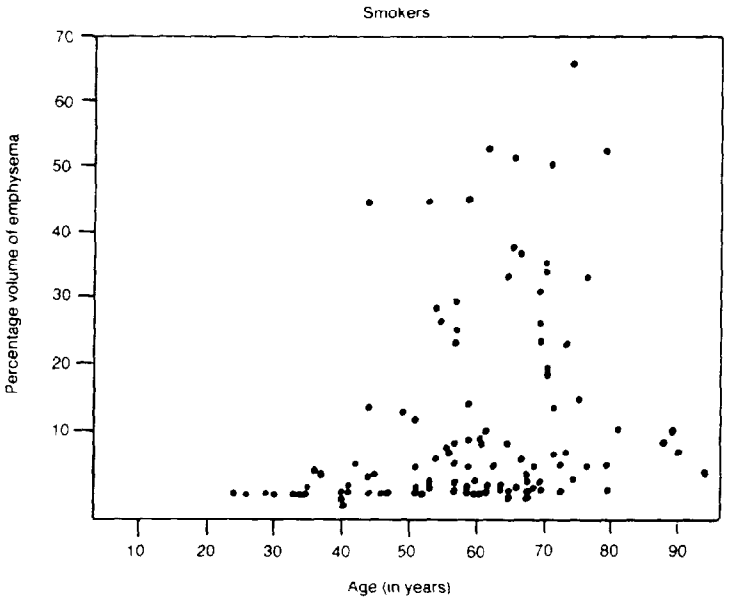

FIGURE 7.—Percentage of lung occupied by emphysema in smokers

SOURCE: Ryder et al. (1971).

in smokers of more than a pack. In women the incidences in the same categories were 0, 17, and 23 percent, respectively. Bonfiglio and Schenk (1974) found that the diagnosis of emphysema was made in 40 percent of autopsy protocols from smokers and in 12 percent from nonsmokers.

Using the autopsy populations of teaching hospitals in three separate cities, Thurlbeck et al. (1974b) reported the average emphysema score per decade for male and female nonsmokers (Figure 8) and for male and female smokers combined with ex-smokers (Figure 9). The severity of emphysema is expressed using the panel grading method (Thurlbeck et al. 1970). With this method, a score of up to 25 is "mild emphysema." As Figure 8 indicates, in nonsmokers there is an increasing average severity of emphysema with age, starting in the fifth decade, reaching an average score in the eighth and ninth decades of 10 to 15 in men and 4 to 6 in women. There is a dramatic difference in male heavy smokers and ex-smokers, for whom the average score of 25 to 30 in the seventh decade is maintained for the next two decades. The number of heavy smoking and ex-smoking women is very small, and the effects in

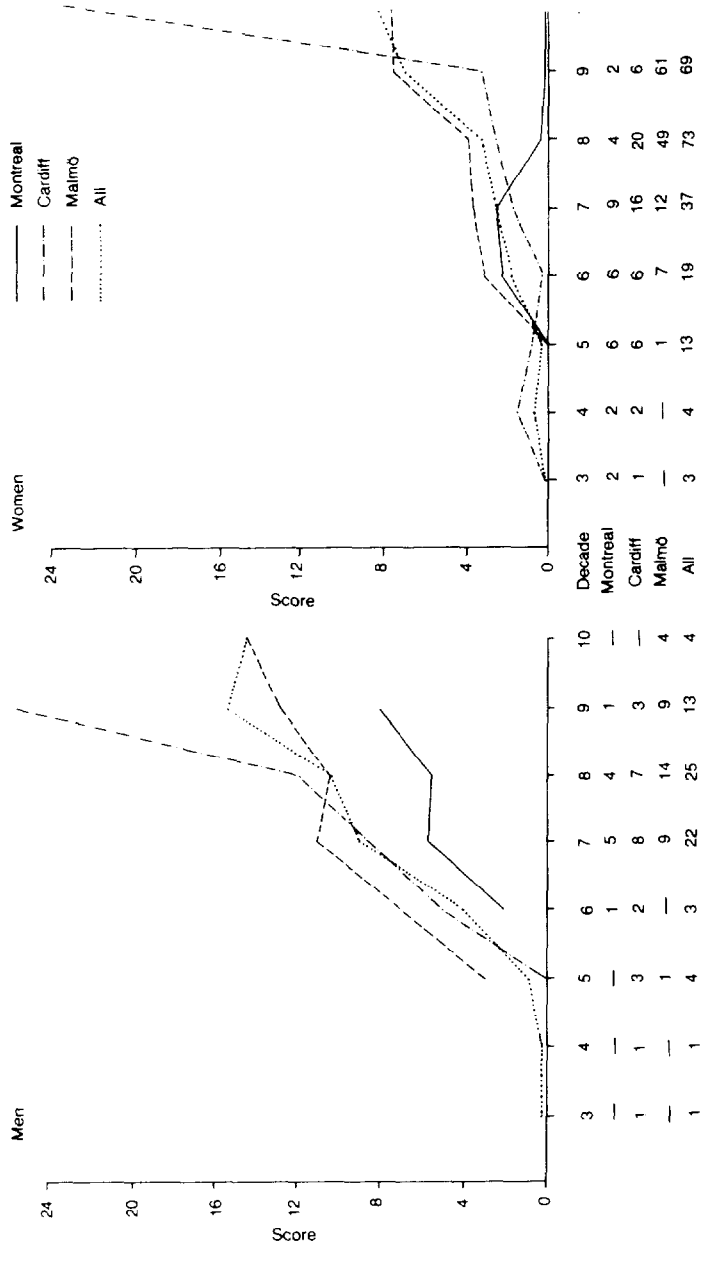

FIGURE 8.—Average emphysema score in male and female nonsmokers in Montreal, Cardiff, and Malmö, by decade

NOTE: All: The average for the three cities.
SOURCE: Thurlbeck et al. (1974b).

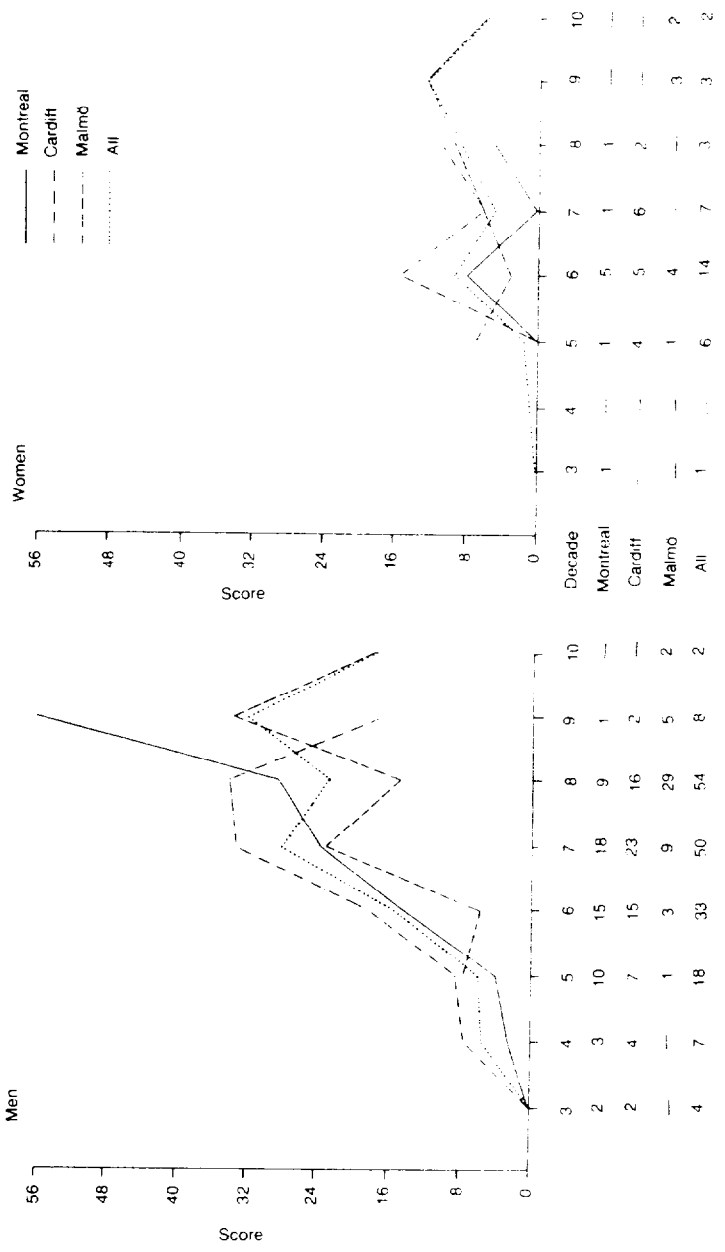

FIGURE 9.—Average emphysema score in male and female heavy cigarette smokers (>pack per day) and ex-smokers, by decade

NOTE: All: The average for the three cities.
SOURCE: Thurlbeck et al. (1974b).

women are more modest, with an average emphysema score of 8 to 12 from the sixth to the ninth decade.

Pratt et al. (1980) studied the effect of smoking on cotton textile workers and on workers not exposed to cotton. They found that the incidence of centrilobular emphysema was 6.7 percent in nonsmoking non-cotton-textile workers, 6.9 percent in nonsmoking cotton-textile workers, 26.5 percent in smoking non-cotton-textile workers, and 26.2 percent in smoking cotton-textile workers. The variation in the incidence of centrilobular emphysema involving more than 25 percent of the lung was even more dramatic—1.1, 0.4, 11.0, and 12.6 percent for the respective categories.

Thus, despite the limitations in interpretation of the types of emphysema and in recognition of the presence of emphysema, the association between smoking and emphysema—particularly severe emphysema—is overwhelming. In the various series referred to, of the 227 patients with severe emphysema, only 3 were nonsmokers.

Summary and Conclusions

1. Smoking induces changes in multiple areas of the lung, and the effects in the different areas may be independent of each other. In the bronchi (the large airways), smoking results in a modest increase in size of the tracheobronchial glands, associated with an increase in secretion of mucus, and in an increased number of goblet cells.
2. In the small airways (conducting airways 2 or 3 mm or less in diameter consisting of the smallest bronchi and bronchioles) a number of lesions are apparent. The initial response to smoking is probably inflammation, with associated ulceration and squamous metaplasia. Fibrosis, increased muscle mass, narrowing of the airways, and an increase in the number of goblet cells follow.
3. Inflammation appears to be the major determinant of small airways dysfunction and may be reversible after cessation of smoking.
4. The most obvious difference between smokers and nonsmokers is respiratory bronchiolitis. This lesion may be an important cause of abnormalities in tests of small airways function, and may be involved in the pathogenesis of centrilobular emphysema. The severity of emphysema is clearly associated with smoking, and severe emphysema is confined largely to smokers.

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