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## **CHAPTER 2**

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### **Nonneoplastic Bronchopulmonary Diseases**

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## Introduction

The term chronic obstructive bronchopulmonary disease (COPD), as used within this report, refers to chronic bronchitis and pulmonary emphysema. The following is a brief summary of the major relationships between smoking and nonneoplastic bronchopulmonary disease which have been presented in previous reports of the health consequences of smoking (91, 92, 93, 94, 95, 96).

Epidemiological and clinical studies have established cigarette smoking as the most important cause of COPD in the United States. Cigarette smokers have higher death rates from pulmonary emphysema and chronic bronchitis and more frequently have impaired pulmonary function and symptoms of pulmonary disease than nonsmokers. Respiratory infections are more prevalent and more severe among cigarette smokers, particularly heavy smokers, than among nonsmokers. Cigarette smokers appear to develop postoperative pulmonary complications more frequently than nonsmokers. The risk of developing or dying from COPD among pipe or cigar smokers is higher than that of nonsmokers, but it is clearly lower than that among cigarette smokers. Ex-smokers have lower death rates from COPD than do continuing smokers. Cessation of smoking is associated with improved ventilatory function and decreased pulmonary symptom prevalence. Young cigarette smokers of high school age have impaired ventilatory function compared to nonsmoking peers.

For most of the United States population, cigarette smoking is a much greater factor in the development of COPD than air pollution or occupational exposure. Cigarette smoking may, however, act conjointly with atmospheric pollution or occupational exposure to produce greater mortality and morbidity from COPD than would occur from one exposure factor alone.

A genetic error, homozygous alpha<sub>1</sub>-antitrypsin deficiency, present in approximately 1 in 3,600 people in the United States, has been associated with the early development of severe panacinar emphysema. Available evidence does not permit a firm conclusion about the nature of the interaction between smoking and this condition.

Autopsy studies have demonstrated that smokers who die of diseases other than COPD have histologic changes characteristic of COPD more frequently than do nonsmokers.

Experiments in both animals and humans have demonstrated that the inhalation of cigarette smoke is associated with acute and chronic changes in ventilatory function and pulmonary histology. Cigarette smoking exerts an adverse effect on the pulmonary clearance mechanisms including ciliary and macrophage function.

The effect of cigarette smoking on nonneoplastic bronchopulmonary disease has been examined in detail in a number of recently published epidemiological, pathological, and experimental studies.

### *COPD Mortality and Morbidity*

Reid (70) reported that age-adjusted mortality rates from chronic nonspecific lung disease (ICD 502, 526, 527) among British citizens varied with migration patterns. British males living in the United Kingdom had a death rate of 125 per 100,000, whereas migrants to the United States experienced a mortality rate of only 24 per 100,000, which is similar to the mortality rate from chronic nonspecific lung disease found in the U.S. population. The possibility that this variation was due to significant differences in diagnostic criteria was in part ruled out by the finding that standardized morbidity surveys of both populations demonstrated differences in morbidity rates that were similar to the observed differences in mortality rates. The prevalence of respiratory symptoms increased in proportion to the number of cigarettes smoked per day. Cigarette smoking and air pollution were identified as the major factors contributing to the real excess in bronchitis morbidity experienced by the British in the United Kingdom.

Freour and Coudray (23) investigated the prevalence of respiratory symptoms and chronic bronchitis among a random sample of 4,000 men and women between the ages of 30 and 70 who were residents of Bordeaux, France. A standardized questionnaire was administered and measurements of pulmonary function taken. The prevalence of chronic bronchitis increased with age and cigarette smoking. In each age category, smokers had more chronic bronchitis than did nonsmokers. The greater the number of cigarettes smoked per day and the greater the lifetime number of cigarettes smoked, the higher was the prevalence of chronic bronchitis. Coudray, et al. (13), in a study of 1,357 women in the Bordeaux Study, reported a prevalence of morning cough of 1.12 percent among nonsmoking women and 8.91 percent among women who smoked.

Racoveanu, et al. (66) studied the prevalence of chronic bronchitis in 300 residents of a mountainous region and a low-lying delta area in

Romania. Both areas were free of air pollution. The prevalence of chronic bronchitis was higher in the mountains than in the lowlands, and although a definite association between chronic bronchitis and smoking was found in both areas, smoking patterns could not completely account for the differences observed.

Several papers have been recently published (24, 25, 26, 37, 55, 100) comparing respiratory symptoms, such as cough and sputum production, among smokers and nonsmokers in different populations. In each study, respiratory symptoms and disease were more common among cigarette smokers than nonsmokers. Most of these studies (24, 26, 37, 100) demonstrated a dose-response relationship between smoking and symptoms for the amount smoked as measured by the number of cigarettes smoked per day, the lifetime number of cigarettes, or the degree of inhalation.

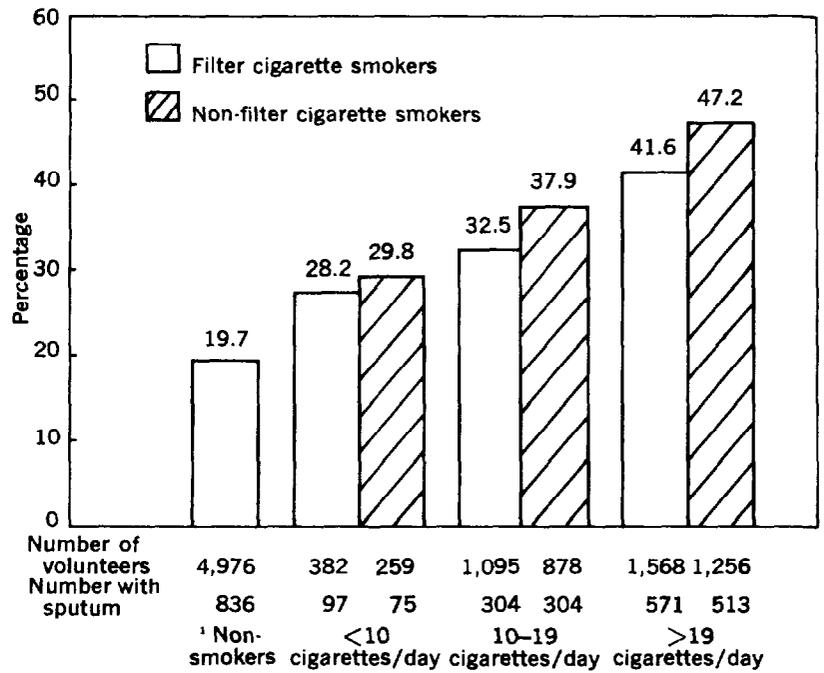
The spontaneous development of a pneumothorax with the resultant collapse of a lung is often produced by rupture of an emphysematous bleb on the pleural surface. Fournier and Zivy (21) reviewed 61 cases of spontaneous pneumothorax. The smoking habits of these patients were compared with those of matched controls. Spontaneous pneumothorax after the age of 25, was strongly associated with cigarette smoking. Zivy (101) further characterized 40 of these cases.

#### FILTER CIGARETTES

The effect of smoking plain and filtered cigarettes on the prevalence of sputum production was examined by Rimington (71). A total of 10,414 volunteers aged 40 and older were studied by questionnaire and chest X-ray. Of this group, 3,045 smoked filter cigarettes and 2,393 smoked nonfilter cigarettes. The rate of persistent daily sputum production was 31.9 percent in filter cigarette smokers and 37.2 percent in smokers of nonfilter cigarettes. The difference is significant ( $P < 0.001$ ). Although there was an increase in sputum production with the amount smoked in both groups, the difference between filter and nonfilter smokers was maintained irrespective of the amount smoked (fig. 1). The author observed, "While there is no doubt that smokers of any type of cigarette are liable to develop chronic bronchitic symptoms such as persistent phlegm, it seems likely that those plain cigarette smokers who are unable to stop smoking cigarettes would suffer less if they smoked filter brands of comparable size."

The effect of smoking modified cigarettes on respiratory symptoms and ventilatory capacity was examined by Freedman, et al. (22). Six hundred men between the ages of 25 and 54 who smoked at least 10 cigarettes a day and had symptoms of chronic bronchitis were divided into three equal groups matched by age, pulmonary function, cigarette consumption, and cough frequency. The individuals were provided

Figure 1.—Age-standardized percentage of chronic sputum production in males by amount smoked and type of cigarette.



<sup>1</sup> Includes ex-smokers and non-cigarette smokers.

SOURCE: Rimington, J. (71).

with test cigarettes "A," "B," or "C." All the test cigarettes contained 1.65 mg. of nicotine. "A" delivered 22 mg. of tar, and "B" and "C" 17 mg. of tar. In addition, "C" had approximately a 50 percent reduction in the vapor phase constituents. Those provided with cigarette "C" increased the average number of cigarettes smoked by about 10 percent, where consumption eventually leveled off. After 4 months, men smoking cigarette "C" began to have lower average cough frequency scores than the others. Significant changes did not occur in sputum production or pulmonary function. The authors observed that, " \* \* \* modification of the composition of cigarettes and their filters can reduce smokers' cough, an important and early symptom of bronchitis."

#### PULMONARY FUNCTION

Results of studies of pulmonary function and smoking from several countries, including India (65), Turkey (2), Germany (7, 34, 38), and Great Britain (41) indicate that cigarette smokers have diminished average pulmonary function compared to nonsmokers. The various measures of pulmonary function used included vital capacity, expiratory reserve volume, residual volume, residual functional capacity, maximum voluntary ventilation, forced expiratory volume in 1 second, and peak expiratory flow rate.

Other studies in which both pulmonary function and respiratory symptoms are considered (27, 30, 36, 43, 59, 69) have again confirmed that smoking is associated with an increase in pulmonary symptoms and a decrease in pulmonary function.

Ex-smokers experience a decrease in the prevalence of respiratory symptoms and an improvement in pulmonary function compared to continuing smokers. These effects have been noted in several recent studies (36, 37, 43).

Ulmer (87) conducted a survey of respiratory symptoms in a random sample of 2,444 individuals between the ages of 10 and 70 years in Duisburg, Germany. The prevalence of chronic bronchitis as measured by cough and/or sputum production in the morning or throughout the day increased with advancing age and with increasing cigarette consumption ( $P < 0.001$ ).

Latimer, et al. (48) studied the ventilatory patterns and pulmonary complications of 46 patients following elective upper abdominal surgery. Factors that favored the development of postoperative macroatelectasis included smoking, obesity, and prolonged anesthesia.

Teculescu and Stanescu (84) examined several measures of pulmonary function in 44 asymptomatic young men between the ages of 18 and 29 in Romania. No significant differences were found between the smokers and nonsmokers. This may have been due to the selection of asymptomatic subjects for examination and relatively insensitive measures of early airway obstruction.

### *Occupational Hazards*

#### BYSSINOSIS

Byssinosis is a respiratory disease found in cotton, flax, and hemp workers. The earliest manifestations of this disease are shortness of breath, cough, and chest tightness. Initially, symptoms occur only upon reexposure to cotton dust at the beginning of the work week. In more advanced form, byssinosis is associated with permanent and occasionally severe airway obstruction, which may force the worker to change his occupation (31). Abnormalities in pulmonary function tests reflect the severity of the symptoms; however, chest films of workers with byssinosis reveal no characteristic findings. McKerrow and Schilling (54) first suggested that byssinosis may occur more frequently among smokers than nonsmokers. Several relatively recent studies have clarified the relationship between smoking and byssinosis. Bouhuys, et al. (8) found 61 cases of byssinosis in 214 male workers in the carding and spinning rooms of a cotton mill. The prevalence of

byssinosis symptoms was higher among cigarette smokers than in nonsmokers ( $P < 0.025$ ).

Szymczykiewicz, et al. (82) found a higher prevalence of chronic nonspecific pulmonary symptoms among smokers than nonsmokers in a study of 3,167 cotton mill workers in Poland.

An examination of 500 cotton textile workers by Schrag and Gullett (75) disclosed 63 individuals with byssinosis; 57 percent (36 workers) of those with byssinosis smoked more than a pack of cigarettes a day, whereas only 34 percent (152 workers) of those without byssinosis smoked this amount ( $P < 0.001$ ).

Merchant, et al. (58) conducted a study of byssinosis in a yarn mill in North Carolina; 25 employees with byssinosis were identified in a population of 441 workers. A scale of 0 to 3 (based on 5 weighted questions concerning cough, breathlessness, and chest tightness on Monday mornings) was used to indicate the degree of severity of byssinosis among the working population. The effect of cigarette smoking on this byssinosis index is apparent (table 1). Among the employees with high exposure to cotton dust, no nonsmokers had a byssinosis index rating over 1, but nearly 18 percent of those currently smoking had ratings of 2 or 3. The effect of smoking alone on the byssinosis index is significant ( $P < 0.01$ ). Also, the interaction between current smoking and current exposure-risk on the byssinosis index is highly significant ( $P < 0.005$ ). Women in this study were exposed to lower levels of respirable cotton dust, and among them no age, smoking, or exposure-risk effects were demonstrated. Smoking among males also had a significant effect on the bronchitis index ( $P < 0.002$ ). Spirometry results on 134 males and 100 females were categorized by sex, age, and smoking history. Among men, the greatest impairment

TABLE 1.—Percent prevalence of byssinosis for men by index of severity and smoking habits (numbers in parentheses indicate number of cases in exposure-risk group)

	Index rating (see text)	Percentage of subject		
		Never smoked (23)	Current smokers (85)	Ex-smokers (21)
Severe.....	3	0	14	5
Moderate.....	2	0	4	5
Mild.....	1	22	26	29
None.....	0	78	57	62
Total.....		100	100	100

Source: Merchant, J. A., et al. (58).

was observed among the smokers who worked in the high exposure-risk areas. The mean FEV<sub>1</sub> for 66 men in this category was only 76 percent of predicted, and their FVC was 90 percent of predicted. Nonsmoking men in both the high- and low-exposure areas had better pulmonary function than their smoking coworkers.

#### EXPOSURE TO ASBESTOS

Langlands, et al. (45) surveyed respiratory symptoms, pulmonary function, and radiological findings among 252 asbestos insulation workers in Belfast, Ireland. Respiratory symptoms of cough, sputum production, and wheezing were much more frequent in smokers. Of the tests for pulmonary function, the peak flow rate and forced expiratory volume at 1 second were most impaired in cigarette smokers. Although little difference was reported in the X-ray findings of smokers and nonsmokers, smokers of more than 25 cigarettes a day had a 20-percent reduction in pulmonary function as measured by these tests.

Lung function and pulmonary symptoms in 1,015 chrysotile asbestos mine and mill workers in Quebec were studied by Becklake, et al. (6) and McDonald, et al. (53). An analysis of respiratory symptoms indicated that shortness of breath was more closely related to dust exposure than to smoking. However, cough, wheezing, and sputum production were much more frequent in smokers than nonsmokers. Pulmonary function was assessed by measuring lung volumes, flow rates, and diffusing capacity. The best pulmonary function was found in nonsmokers with low dust exposure while smokers with high dust exposure had lower pulmonary function values.

In a survey of 201 asbestos workers, Regan, et al. (67) investigated the relative power of 16 clinical, radiological, and pulmonary function variables including smoking for differentiating between asbestosis and chronic obstructive airway disease. Cigarette smoking was not a characteristic that could be used to separate these conditions.

#### EXPOSURE TO COAL DUST

The spectrum of pulmonary reactions to coal dust was reviewed in a volume edited by Key, et al. (40). Hunter (33) noted that coal miners who smoked experienced a higher prevalence of respiratory symptoms (cough, sputum production, breathlessness, and wheezing) and developed them earlier than nonsmoking miners. Their pulmonary function tests also tended to show greater impairment than those of nonsmokers. Lainhart and Morgan (44) reported that coal miners had an increase in persistent productive cough with increasing years of exposure to coal dust. This effect was magnified by cigarette smoking independent of age or years of underground work. In an autopsy

study, Naeye (62) observed more right ventricular hypertrophy and a higher emphysema index in smoking miners than in nonsmoking miners. In commenting on the etiology of pulmonary reactions in coal miners, Lee (49) felt that smoking in coal miners probably facilitated the development of bronchitis and emphysema, rather than participating in the genesis of the characteristic lesion of coal workers' pneumoconiosis.

The prevalence of chronic bronchitis in 3,012 ex-coal miners and 9,361 nonminers of similar age and social class was examined by Lowe and Khosla (51). All were employed at the time of the investigation in two steel works in South Wales. The ex-miners had substantially more chronic bronchitis and more impaired ventilatory capacity than the nonminers irrespective of age and smoking habits. The prevalence of chronic bronchitis was 24.9 percent in smoking ex-miners and 12.0 percent in nonsmoking ex-miners. The prevalence was 18.6 percent and 7.7 percent in smoking and nonsmoking nonminers, respectively. In this study, smoking appeared to be a more important factor for the development of chronic bronchitis than coal mining or age.

Haber, et al. (29) studied cigarette smoking, dust inhalation, and sputum production as factors in the etiology of chronic bronchitis among 479 coal miners and 166 farmers in Hungary. In both the miners and the farmers, there was a significantly higher proportion of chronic bronchitis cases among smokers than among nonsmokers, and the proportion of bronchitics increased with the number of cigarettes smoked. Cigarette smoking was found to be a more important factor in the etiology of bronchitis than dust inhalation.

Lapp, et al. (46) examined changes in several measures of ventilatory capacity in 93 coal miners and 42 nonminers before and after a work shift. Following the shift, small but significant decreases in ventilatory capacity occurred among the miners ( $P < 0.05$ ), while significant increases in ventilatory capacity occurred among the nonminers ( $P < 0.05$ ). Decreases in pulmonary function tests were related to the dust exposure of the miners; however, the greatest decreases in pulmonary function occurred among the smokers.

Seaton, et al. (76) examined several measures of pulmonary function in 214 coal workers who had radiologic evidence of CWP with lung opacities that ranged in size from less than 1.5 mm. to 3 mm. in diameter. They found no significant difference in pulmonary function between the 102 smokers and 112 nonsmokers with coal workers' pneumoconiosis. Similar results were reported by Lyons, et al. (52).

Hyperinflation of the lungs in coal miners was studied by Morgan, et al. (61). Residual volumes, total lung capacities, and chest X-rays of 1,455 working Pennsylvania coal miners were examined. The relationship between radiographic evidence of coal workers' pneumoconiosis and lung volumes was investigated. The residual volume in-

creased with radiographic category, obstruction to air flow, and cigarette smoking. Each of these factors had a separate and additive effect that resulted in an increased residual volume.

Ulmer (86) examined a random sample of the working population in the Ruhr area of West Germany. Measurements were made of the total lung capacity, airway resistance, and arterial oxygen saturation. All coal miners had larger total lung capacities than workers without dust exposure. Smokers had significantly larger volumes than nonsmokers ( $P < 0.05$ ).

Lapp, et al. (47) examined pulmonary hemodynamics in 47 asymptomatic coal miners. They were divided into two groups depending upon the absence or presence of airway obstruction. Pulmonary hypertension was more frequent in the group with obstruction. The group of 23 men (mean age 51 years) without airway obstruction, had an average cigarette consumption of 17 pack-years per miner, whereas the group of 24 men (mean age 56 years) with airway obstruction averaged 31 pack-years per miner.

From the work of several investigators it can be concluded that cigarette smoking is an important factor in the development of respiratory disease other than pneumoconiosis, among coal miners (29, 40, 46, 47, 51, 61, 86). There is no consensus in recent publications on what role cigarette smoking may play in the development of coal workers' pneumoconiosis (40, 61, 76).

#### MISCELLANEOUS EXPOSURES

The effect of cigarette smoking on pulmonary function in jet fighter pilots and crew members was examined by Browning (9). At high altitudes, 100-percent oxygen is delivered under low pressure to the aircrew members in order to maintain adequate blood oxygen levels. The vital capacity was acutely compromised in flight on the 100-percent oxygen mixture. This was especially true under high G (gravity) conditions. Smokers had a significant inflight volume loss that was three and one-half times that noted among the nonsmokers under these conditions ( $P < 0.05$ ). Recovery of normal vital capacity following flight was also delayed in the smokers.

Gregory (28) reviewed 340 cases of chronic bronchitis that occurred among the employees of the Sheffield steelworks in England. Smoking was associated with a high prevalence of chronic bronchitis, but of particular interest was the effect of cigarette smoking on disability. The interval between the onset of chronic bronchitis and disability from this disease was significantly less ( $P < 0.02$ ) for those smoking more than 20 cigarettes a day than for nonsmokers and for those smoking less than this amount ( $P < 0.02$ ).

Batawi (5) examined the prevalence of several diseases including

respiratory illnesses in 4,643 employees in Egypt, comprising a 5.3 percent sample of 92,000 employees in 17 major industries. Respiratory illnesses occurred more frequently in all segments of the cotton industry, as well as leather, printing, and glass industries; 40 percent of all employees were smokers, and they experienced higher rates of respiratory symptoms and illnesses than nonsmokers. Smokers with occupational exposure to dust were particularly affected.

The effect of cigarette smoking and occupational exposure to dust on the prevalence of chronic bronchitis was examined by Golli (25) in Romania. There were 2,942 individuals examined of whom 142 were employed in dusty occupations. Chronic bronchitis was present in 24.6 percent of the 457 smokers and 4.4 percent of the 2,343 nonsmokers ( $P < 0.001$ ). Increasing age, cigarette smoking, and occupational exposure to dust each independently contributed to an increased prevalence of chronic bronchitis.

Recent studies in metal casting, plaster, coke, baking, agricultural, and chemical industries have documented a higher incidence of respiratory symptoms and/or diminished pulmonary function among cigarette smoking workers than nonsmoking workers (42, 64, 89, 97, 99).

### *Air Pollution*

Reichel and Ulmer (68, 88) examined the effect of air pollution on the prevalence of respiratory disease among 8,162 men and women in West Germany. The three areas chosen for study had widely different atmospheric levels of sulphur oxides and particulate matter. The frequencies of cough and sputum production were the same within the nonsmoking groups in all three areas. No differences were found in pulmonary function or arterial blood gases between subjects of the three districts. Smokers in each area had a higher prevalence of respiratory symptoms than nonsmokers. The authors concluded, "There is no doubt that the influence of air pollution is less important than that of age, sex, and smoking habits."

Tsunetoshi, et al. (85) examined the prevalence of chronic bronchitis in Osaka, Japan. The independent contributions of age, smoking habits, and air pollution were examined. In male cigarette smokers using more than a pack a day, chronic bronchitis was three to four times more prevalent than in nonsmokers. In female smokers using half a pack or more a day, chronic bronchitis was five to six times more prevalent than in nonsmokers. The standardized prevalence of chronic bronchitis increased with the degree of air pollution, particularly sulphur dioxide pollution, but not with increasing levels of suspended particulate matter.

The Federal Aviation Administration, Department of Transportation, and the National Institute for Occupational Safety and Health jointly conducted a study of the levels of certain combustion byproducts of tobacco on military and civilian aircraft produced by passengers' smoking and also asked the passengers for their subjective reaction to tobacco smoke (90). Levels of carbon monoxide, particulate matter, polycyclic hydrocarbons, ammonia, and ozone were measured on 20 military and eight domestic flights. On all aircraft the measured level of each substance was much lower than recommended occupational and environmental air quality standards. This was probably the result of the efficient ventilation systems required on all aircraft (20 exchanges of cabin air each hour).

More than 60 percent of the passengers reported that they were bothered by tobacco smoke and suggested that corrective action such as segregation of smokers and nonsmokers be taken. More than 70 percent of the nonsmokers who had a history of respiratory conditions were annoyed by tobacco smoke. The discomfort attributed to tobacco smoke in spite of the efficient ventilation system might have reflected crowded seating conditions or drying of the respiratory membranes which results from the very low humidity found on most aircraft.

### **Autopsy Studies**

Auerbach, et al. (4) studied the relationship between age, smoking habits, and emphysematous changes in whole lung sections obtained at autopsy from 1,443 males and 388 females. A total of 7,324 sections 1 mm. thick were graded on a scale of 0 to 9 according to the severity of emphysema. No distinction was made between centrilobular and panlobular emphysema. The men were classified by age, type of smoking (pipe, cigar, or cigarette), and amount of cigarette smoking. Smoking habits were ascertained by interviews with relatives. Within each of the six smoking categories, the mean degree of emphysema increased with age. Adjusting the data for age revealed that the mean degree of emphysema was lowest among men who never smoked, was higher in pipe or cigar smokers, and highest among regular cigarette smokers. A dose-response relationship was found for the number of cigarettes smoked per day and the severity of emphysema. Table 2 and figure 2 show these relationships.

Fingerland, et al. (19) investigated the prevalence of various pathological conditions including emphysema and chronic bronchitis in an autopsy population comprising all persons over the age of 20 who came to autopsy over a 2-year period at the Institute of Pathological Anatomy in Czechoslovakia: 765 males and 573 females were included

in the study. Smoking histories were obtained from patients before death, medical records, or relatives. The smokers were divided into three groups based upon the number of cigarettes smoked during their lifetime; 26 percent of the male nonsmokers showed some evidence of emphysema, whereas 70 percent of male smokers of more than 500,000 lifetime cigarettes showed these changes (fig. 3). Similar relationships were demonstrated for chronic bronchitis.

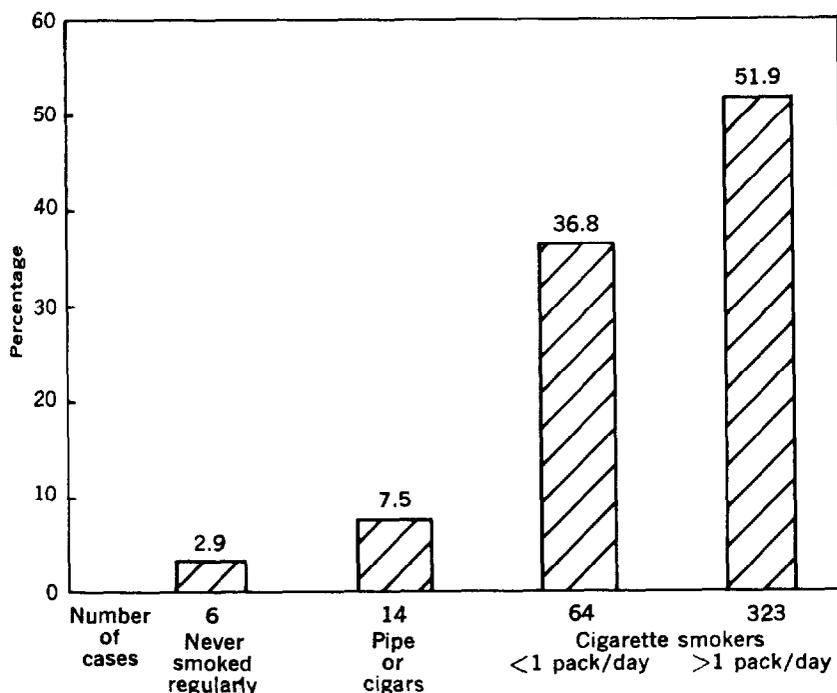
TABLE 2.—Degrees of emphysema in current<sup>1</sup> smokers and in nonsmokers according to age groups

Age group and degree of emphysema (see text)	Subjects who never smoked regularly	Current pipe or cigar	Packages smoked per day			
			<½	½ to 1	1 to 2	>2
<b>&lt;60:</b>						
0 to 0.75.....	53	18	12	3	2	0
1 to 1.75.....	2	11	4	9	24	5
2 to 2.75.....	0	1	2	17	130	56
3 to 3.75.....	0	1	5	12	50	38
4 to 4.75.....	0	0	0	4	8	7
5 to 6.75.....	0	0	0	0	4	5
7 to 9.00.....	0	0	0	0	3	1
Totals.....	55	31	23	45	221	112
Mean.....	.10	.83	1.29	2.37	2.56	2.86
SD.....	.04	.13	.26	.16	.07	.10
<b>60 to 69:</b>						
0 to 0.75.....	35	17	4	0	0	0
1 to 1.75.....	1	8	1	0	4	1
2 to 2.75.....	2	3	4	5	37	23
3 to 3.75.....	2	2	2	9	42	24
4 to 4.75.....	0	0	1	3	11	9
5 to 6.75.....	0	0	0	1	8	1
7 to 9.00.....	0	0	0	1	5	4
Totals.....	40	30	12	19	107	62
Mean.....	.39	.95	1.90	3.59	3.39	3.37
SD.....	.13	.16	.34	.35	.15	.20
<b>70 or older:</b>						
0 to 0.75.....	68	21	2	0	0	0
1 to 1.75.....	4	28	10	8	2	2
2 to 2.75.....	5	22	13	23	40	9
3 to 3.75.....	4	8	5	10	38	18
4 to 4.75.....	0	2	1	7	11	7
5 to 6.75.....	0	1	0	2	9	3
7 to 9.00.....	0	0	0	1	12	5
Totals.....	81	82	31	51	112	44
Mean.....	.50	1.66	2.15	2.98	3.68	3.91
SD.....	.39	.11	.17	.20	.17	.27

<sup>1</sup> Subjects who smoked regularly up to time of terminal illness.

Source: Auerbach, O., et al. (4).

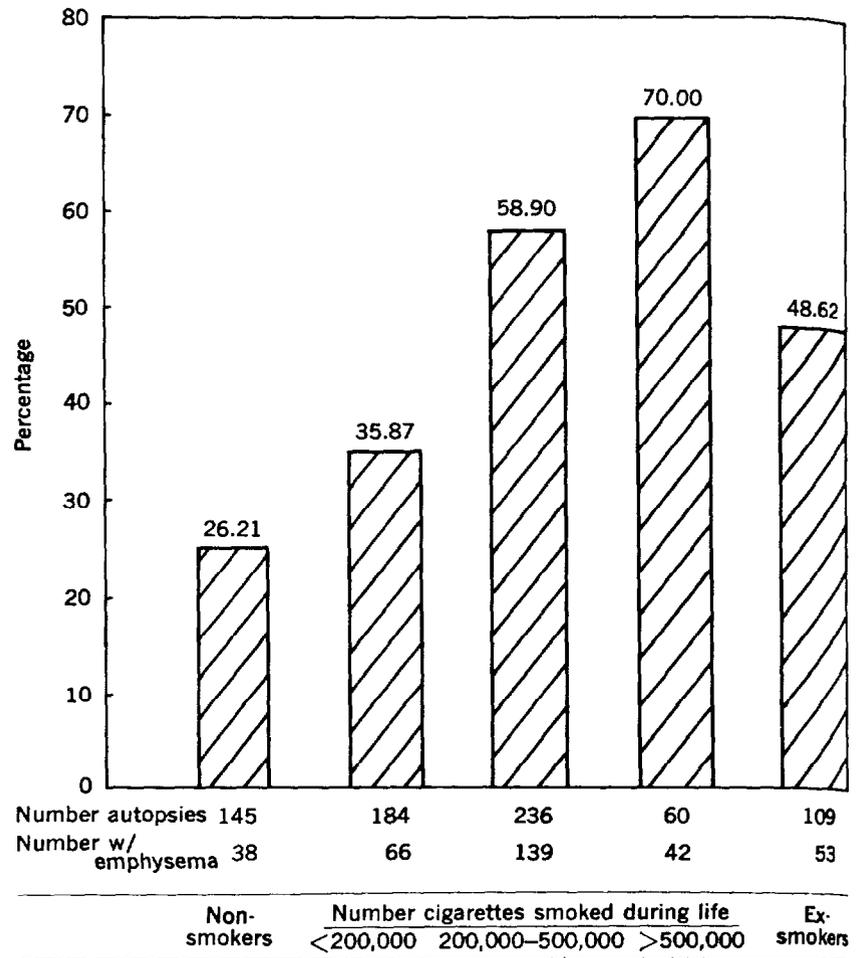
Figure 2.—Age-standardized percentage distribution of whole lung sections of males with moderate to far-advanced emphysema (score 3–9) by smoking category.



SOURCE: Auerbach, O., et al. (4).

Mitchell, et al. (60) conducted a study to determine the accuracy of the recorded cause of death on death certificates of adults; 578 autopsies were performed on patients 40 years of age and older at two large hospitals in Colorado. In addition, 409 patients with COPD were enrolled in an emphysema registry. Autopsies were performed on the 56 patients who died during the study period. Death certificates were obtained from the State Health Department, and the recorded cause of death was compared with the autopsy findings. In 211 of the 634 autopsies performed, the cause of death was found to be COPD; however, in only 160 of these cases (76 percent) was COPD listed as the cause of death on the death certificate; 3 percent of death certificates incorrectly listed emphysema as a cause of death when this was not supported by autopsy evidence. The authors concluded their study by suggesting “\* \* \* that national statistics, which are based on non-autopsy confirmed diagnoses, might understate deaths from chronic bronchitis and ‘emphysema.’”

Figure 3.—Prevalence of emphysema in adult males at autopsy by smoking category.



SOURCE: Fingerland, A., et al. (19).

## Experimental and Histopathological Studies

### *Histopathological Studies*

#### Studies in Man

Naeye and Dellinger (63) examined the small pulmonary arteries of 126 male cigarette smokers and 67 nonsmokers for quantitative changes in collagen, elastic tissue, and circularly and longitudinally oriented smooth muscle. They found a progressive increase in collagen

and longitudinally oriented smooth muscle fibers and a progressive decrease in circularly oriented muscle fibers with age. These changes were more advanced at each age in smokers than in nonsmokers ( $P < 0.01$ ).

Sobonya and Kleinerman (78) quantified the smooth muscle and mucous glands in the bronchi of 13 male cigarette smokers and 11 male nonsmokers from Ohio who were 18 to 46 years old and had died of nonrespiratory causes. The smokers averaged 24 pack-years of exposure. Although the smokers had a history of more respiratory symptoms and colds than the nonsmokers, no difference was found in the percentages of smooth muscle or bronchial glands between smokers and nonsmokers. Five of the 13 smokers showed evidence of squamous metaplasia.

Ellefsen and Tos (17) determined the goblet cell density in tracheal biopsies from 50 patients with respiratory symptoms or disease. Goblet cell density increased with symptoms of tracheobronchitis and history of exposure to dust. A slight increase was also noted in mean goblet cell density with increasing consumption of cigarettes from 136 in symptomatic nonsmokers to 154 in smokers of more than a pack a day.

#### Studies in Animals

Syzganov, et al. (81) exposed 55 dogs to cigarette smoke inhaled through tracheostomas for periods of up to a year or longer. An additional 15 dogs served as nonsmoking controls. The smoking animals developed bronchitis, bronchopneumonia, interstitial pneumonia, and hyperplasia of the bronchial epithelium. Later histologic changes included squamous metaplasia and papilloma formation not found in controls.

The effect of sulphur dioxide ( $\text{SO}_2$ ) and cigarette smoke on the mucous glands of rats and the bronchial glands of lambs was studied by Mawdesley-Thomas, et al. (57). There was a slight increase in the goblet cell count of rats with the inhalation of  $\text{SO}_2$  and cigarette smoke. Exposure of lambs to cigarette smoke inhaled through a tracheostoma resulted in hypertrophy of the bronchial glands.

Jones, et al. (39) found that the addition of phenylmethyloxadiazole (PMO) to tobacco protects rats against some of the adverse effects of exposure to cigarette smoke. Two groups of 15 Sprague-Dawley rats were exposed to 25 cigarettes a day, 4 days a week for 6 weeks. The group exposed to cigarettes containing PMO showed less immediate distress after exposure and had a lower tracheal goblet cell count, less thickening of the tracheal epithelium, and fewer cells in mitosis than those exposed to the regular cigarettes.

The response of the rat lung to low levels of nitrogen dioxide ( $\text{NO}_2$ ), a constituent of cigarette smoke, was studied by Stephens, Evans, and

their associates (18, 80). Young male rats were continuously exposed to NO<sub>2</sub> at concentrations of 2 p.p.m. and 17 p.p.m. for 1 year. Animals were sacrificed after a short exposure and also at regular intervals over the 12-month period. At the level of 17 p.p.m., destructive changes occurred in the respiratory epithelium within 4 hours. These changes included cell hypertrophy, loss of cilia, and increased mitotic activity. After 24 hours of exposure at this level some repair began, but cuboidal cells replaced the normal respiratory epithelium. At 2 p.p.m. the acute damage was less severe, and complete recovery occurred over a period of several weeks.

Sherwin, et al. (77) studied the effect of low doses of NO<sub>2</sub> on the alveolar wall cells of the guinea pig. They found that continuous exposure of 2 p.p.m. NO<sub>2</sub> produced a significant increase ( $P < 0.05$ ) in the lactate dehydrogenase (LDH) index of the lower lobes of the lung, suggesting that the ultrathin type 1 (LDH positive) alveolar wall cells were being replaced by relatively thick type 2 cells resulting in a physiologically significant blood-gas barrier.

### *Pulmonary Function*

Ingram and O'Cain (35) studied dynamic compliance in nine smokers and nine nonsmokers under the age of 30 who were in good health. Both groups were identical with respect to airway resistances, lung volumes, maximal expiratory flow rates, and static compliance values. Dynamic compliance fell more rapidly in the smokers than in the nonsmokers above a frequency of 40 breaths a minute. The difference was statistically significant ( $P < 0.0001$ ). Isoproterenol produced no significant increase in dynamic compliance in either the smokers or the nonsmokers. In six of the smokers who stopped smoking, the dynamic compliance curves gradually approached the values of the nonsmokers over an 8-week period. Changes over this relatively long period of time indicate that the decrease in dynamic compliance observed in smokers was more likely caused by inflammatory changes or some other mechanism rather than muscular constriction in the bronchioles. The authors concluded that peripheral airway abnormalities are regularly present in young asymptomatic smokers.

The effect of cigarette smoking on pulmonary diffusing capacity was studied by Van Ganse, et al. (98). Diffusing capacity is dependent upon: A membrane component, which is the resistance offered by the lung tissues, and the volume of blood in the lung capillaries. Studies were conducted on 142 randomly selected residents of Berlin, N.H., over the age of 25. In both men and women, there was a decrease in diffusing capacity for carbon monoxide with an increase in age and