

4. Of the studies in which dose-specific prevalence rates were examined, strong dose-response relationships between cigarette smoking and symptoms of COPD were generally demonstrated.

5. The relationship between cigarette smoking and COPD mortality has been demonstrated in the United States, Canada, Great Britain, and Ireland; strong associations between cigarette smoking and COPD morbidity have been shown in the United States, Canada, England, Australia, Finland, Sweden, France, Belgium, Hungary, and Japan.

6. Epidemiologic evidence from many countries indicates that, for both sexes, symptomatic and asymptomatic cigarette smokers have greater impairment of pulmonary function than do nonsmokers.<sup>1</sup>

7. Previous evidence indicates that cessation of smoking results in lower death rates from COPD, improved pulmonary function, and a decrease in the prevalence of pulmonary symptoms.

8. Prospective and cross-sectional analyses of data reveal that pipe and cigar smokers have higher mortality rates from chronic bronchitis and emphysema than do nonsmokers, but lower rates than those of cigarette smokers. Pipe and cigar smokers have a higher prevalence of respiratory symptoms than do nonsmokers. The limited data on pulmonary function studies in pipe and cigar smokers are, thus far, inconclusive.

9. Available data suggest that although air pollution may contribute to the prevalence of symptoms of respiratory disease, cigarette smoking is far more important in producing respiratory disease. Cigarette smoking and air pollution may interact to produce higher rates of pulmonary disease than are seen with either factor alone.

10. Certain occupational exposures result in an increased incidence of COPD, but the relationship is not as strong as for cigarette smoking. The combination of certain occupational hazards and cigarette smoking has been observed, in many studies, to result in additive effects on morbidity from COPD. Exposures to cotton fiber, asbestos, and coal dust, in particular, appear to act in concert with cigarette smoking in the development of pulmonary disease. The role cigarette smoking plays in the development of coal workers' pneumoconiosis is unclear at present.

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<sup>1</sup>In these studies, the degree of the relationship between smoking and impaired pulmonary function was found to be dependent on the sensitivity of the particular pulmonary function test utilized to detect pulmonary obstruction and/or small airways disease, the age, sex, occupation, place of residence, general state of health, and intensity of the smoking habit of the population examined.

11. A genetically determined protease-deficiency (alpha<sub>1</sub>-antitrypsin deficiency), inherited as an autosomal recessive trait, is found as a homozygous deficiency in approximately 1 in 3,600 people and as a heterozygous deficiency in approximately 5 to 8 percent of the population. Those with the homozygous deficiency have an increased prevalence of pulmonary emphysema. It is not clear whether cigarette smoking is an important contributor to the premature development of emphysema in people with the homozygous or heterozygous deficiency states. It is also unknown whether nonsmoking heterozygotes are at a greater risk of developing emphysema than nonsmokers or smokers with normal alpha<sub>1</sub>-antitrypsin activity.

12. Data from most studies implicate cigarette smoking as an important factor in increasing the risk of developing post-operative pulmonary complications.

13. Some data suggest that cigarette smoking may increase the risk of development of spontaneous pneumothorax.

14. Data from pathologic and autopsy studies have demonstrated a dose-response effect of cigarette smoking on the severity of emphysema; pipe and cigar smokers have degrees of emphysema intermediate between those of nonsmokers and cigarette smokers.

15. Goblet cell density and distention, alveolar septal rupture, thickened bronchial epithelium, and mucous gland hypertrophy have been shown at autopsy to be more common in cigarette smokers than in nonsmokers.

16. Experimental data on humans have demonstrated that inhalation of cigarette smoke results in acute impairment of certain parameters of pulmonary function. Overall pulmonary clearance, ciliary function, and alveolar macrophage function have been found to be impaired in smokers as compared to nonsmokers. Some recent data suggest that acute heavy cigarette smoking with deep inhalation may result in increased pulmonary clearance.

17. In animal studies, in vivo and in vitro exposures to whole cigarette smoke (CWS) and several of its components have resulted in impairment in overall pulmonary clearance, ciliary function, and alveolar macrophage function.

18. Experimental data on humans and animals presented in the past suggest that cigarette smoke may impair the function of the pulmonary surfactant system.

Most of the studies reviewed in the last year confirmed the knowledge of the relationship between cigarette smoking and bronchopulmonary disease. A listing of these studies appears in a

separate section of the Supplemental Bibliography. A number of studies extended the knowledge of the association between cigarette smoking and bronchopulmonary disease, but several studies presented data which were either partially or wholly inconsistent with the known relationships; these two types of studies are reviewed below.

## EPIDEMIOLOGIC STUDIES

### *Smoking and COPD*

There have been relatively few studies designed to evaluate the association between cigarette consumption and the prevalence of chronic obstructive pulmonary disease (COPD) in elderly populations. In a random cross-sectional study of 487 men and women between the ages of 62 and 90, living in Edinburgh and registered with a practicing physician, Milne and Williamson (*BP 45, 46*) reported that over 73 percent of the women had never smoked compared with 7.9 percent of the men; 62 percent of the men were current smokers (71 percent of whom inhaled), while only 18 percent of the women were current smokers (50 percent inhalers). In both men and women, a higher percentage of smokers had persistent cough and sputum production than nonsmokers ( $P < .001$  for men and  $P < .01$  for women), but twice the proportion of male smokers had these symptoms than women smokers. A dose-response relationship was demonstrated, since a higher percentage of heavy smokers had these symptoms than lighter smokers ( $P < .01$ ). In men, 12.4 percent of the smokers had persistent cough, sputum, and a recent chest illness; none of the nonsmokers had this combination. For men, significant differences in histories of wheezing and dyspnea were found between smokers and nonsmokers. For women, a significant difference between smokers and nonsmokers was demonstrated only for wheezing ( $P < .05$ ). The authors found that the FEV% (FEV/VC) was below 60 in 32 percent of the men who smoked compared to 6.7 percent of the nonsmokers ( $P < .05$ ). For women, the figures were 9.4 percent and 3.9 percent. This difference was not statistically significant.

In a cross-sectional study of 300 men and women aged 65 and over in Glasgow, Scotland, Caird and Akhtar (*BP 6*) found that among women chronic bronchitis was reported by 11 percent of nonsmokers, 13 percent of light smokers, and 50 percent of heavy smokers. For men, a dose-response relationship was shown for light and heavy smokers, but the small numbers of non-

smokers (5 nonsmokers; 2 with chronic bronchitis) limit the conclusions which can be drawn from the data.

In a retrospective study of 5,438 men aged 40 and over who were current smokers, Rimington (*BP 55*) examined the relationship between the pattern of smoking and the prevalence of chronic bronchitis. He found that for each level of daily consumption of cigarettes, chronic bronchitis was more prevalent among those smokers who kept their cigarettes in their mouths during the entire period of smoking ("droopers") than among those smokers who removed their cigarettes from their mouths between puffs (normals) (table 1). For all levels of consumption, there was a significantly higher prevalence of chronic bronchitis among "droopers" than among normal smokers ( $P < .001$ ). When these values were age-standardized (this was necessary because there was both a higher incidence of bronchitis and a higher percentage of droopers in men over 60 years of age), there was still a higher prevalence of chronic bronchitis among the "droopers" than among the normals, but the statistical significance of this difference was not presented, nor could it be calculated from the data given.

In an analysis of data from Bosnia and Hercegovina in Yugoslavia, Zarkovic (*BP 73*) reported dose-response relationships between depth of cigarette smoke inhalation and prevalence rates for chronic bronchitis, pulmonary emphysema, asthma, cor pulmonale, and clinical and laboratory signs of obstructive lung disease.

TABLE 1.—*Number, percentage, and age-standardized percentage of chronic bronchitics among 5,438 cigarette smoking male volunteers for mass radiography, aged 40 and older, by amount and method of smoking*

	Cigarettes per day							
	1-9		10-19		20+		All	
	D.	N.	D.	N.	D.	N.	D.	N.
Number of volunteers .....	60	581	134	1,839	266	2,558	460	4,978
Number of chronic bronchitics .....	22	150	56	552	113	971	191	1,673
Percentage chronic bronchitics .....	36.6	25.8	41.8	30.0	42.4	37.5	41.5*	33.6*
Age-standardized percentage of chronic bronchitics .....	33.9	26.0	41.1	32.1	44.1	41.1	41.6	35.1

\* $P < .001$ .

D. = "drooping" cigarette smokers. N. = normal cigarette smokers.

SOURCE: Rimington, J. (*BP 55*).

Olzihutag, et al. (BP 50) studied the prevalence of chronic bronchitis in Mongolia and found no association between cigarette smoking and chronic bronchitis in urban women, and a negative association in rural women. These authors found close associations between chronic bronchitis and smoking in men. The authors pointed out that chronic bronchitis increased in frequency with age.

Sherman, et al. (BP 58) conducted a study in Detroit on 489 working men and women, among whom 459 were employed in the auto industry. All subjects were referred to one physician for evaluation for workmen's compensation. The authors concluded that their data challenged "the traditional view (held) by . . . much of the medical profession that workers' lung and heart diseases are largely caused by cigarettes rather than by workplace poisons." These investigators studied various occupational exposures within the auto industry and found that both in exposed and unexposed working populations, approximately the same percentages of cigarette smokers and nonsmokers suffered from bronchitis, emphysema, and heart disease. Imprecise smoking histories and the absence of adjustment for several potentially confounding variables limit the conclusions which can be drawn from these data.

*The Effects of Smoking on Pulmonary Function  
in Patients with COPD*

In a retrospective study of 41 hospitalized cigarette smokers with a diagnosis of pulmonary emphysema, Lepine and Myre (BP 37) found dose-response relationships between number of daily cigarettes smoked and years of dyspnea, years of cough, and impairment of the maximum expiratory flow rate (MEF). No dose-response relationships were found for the presence of cor pulmonale by ECG, X-ray evidence of cardiomegaly, impairment of carbon monoxide diffusion, functional residual capacity, arterial blood gas abnormalities, or the ratio of residual volume to total lung capacity (RV/TLC).

In a retrospective analysis of pulmonary function tests (PFTs) of 140 patients with emphysema, chronic bronchitis, or both, Kass, et al. (BP 31) found no correlation between the severity of impairment of pulmonary function tests and the amount or duration of cigarette smoking.

*The Effects of Smoking on Pulmonary Function in  
Healthy Populations*

Grimes and Hanes (BP 24) studied 1,059 employees of a large insurance company and found that cigarette smoking was associ-

ated with decreases in FVC and FEV<sub>1</sub> for all age groups in men. In women, the younger ex-smokers had higher values on pulmonary function testing than the nonsmokers. Higgins and Keller (BP 26), utilizing data obtained from the Tecumseh Study, did note differences in FVC, FEV<sub>1</sub>, FEV<sub>1</sub>/VC, and MEF<sub>50%</sub> between smokers and nonsmokers for both sexes and between smokers of greater than and less than 20 cigarettes per day. In this study, smokers of either sex had lower mean FVC, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, MEF<sub>50%</sub>, average flow during the middle half of expiration (MMEF<sub>25-75%</sub>), average flow between 0.2 and 1.2 liters of expiration (MMEF<sub>0.2-2L</sub>), and peak expiratory flow rate (PEF) than nonsmokers, and all these values decreased with increasing tobacco consumption.

Krumholz and Hedrick (BP 33) studied pulmonary function in 91 cigarette smoking and 136 nonsmoking "healthy" male executives, aged 35 to 64. They found significant impairment in the smokers for VC (P <.01), FEV<sub>1</sub> (P <.001), FEV% (P <.001), FEV<sub>25-75%</sub> (P <.001), Raw (airway resistance) (P <.05), MVV (P <.05), RV/TLC (P <.05), CO diffusion (D<sub>L</sub>CO) (P <.001), and D<sub>L</sub>CO/TLC% (P <.001). Mean lung volumes were the same in the two groups except for RV/TLC. The methods of selection of patients for this study were not detailed.

Brooks and Waller (BP 2), in a study of 2,703 people attending a public health exhibition, found a nonsignificant difference in peak flow rates between smokers and nonsmokers age 45 and over; no differences were demonstrated for the younger than 45 age groups. The authors pointed out a number of biases which limit the conclusions which may be drawn from these data.

Coleman, et al. (BP 11) investigated the maximal oxygen consumption (physical work capacity) of 78 members of the Texas Tech University faculty and found no difference in this value between smokers and nonsmokers. However, as the authors pointed out, the mean age of the smokers was seven years less than that of the nonsmokers, and the daily activity level of the smokers was also greater than that of the nonsmokers. The combination of these two effects may have partially accounted for the lack of difference in maximal physical work capacity between the smokers and nonsmokers in this study population.

In a cross-sectional study of men and women from the Western Highlands District and Trobriand Islands in New Guinea, Woolcock, et al. (BP 70) found a greater decrease of FVC, FEV<sub>1</sub>, and PEF with age in men who smoked compared to nonsmokers (no P value reported). No such differences were found for women for FEV<sub>1</sub> and PEF.

Woolcock, et al. (BP 69) also reported that in this same group

of New Guineans smoking was not strongly associated with cough on a single examination in the Western Highlands District (WHD) population, but was strongly associated in the Trobriand Islands (TI) population. The authors stated, though, that the TI population smoked western cigarettes, whereas the WHD population smoked predominantly home-grown tobacco rolled in newspaper and smoked as cigars.

*The Roles of Smoking and Pollution in the Development of COPD*

Cigarette smoking is the predominant factor in the development of chronic nonspecific respiratory disease (CNRD), but there have been few prospective studies on the interaction between air pollution and cigarette consumption as risk factors in the development of chronic nonspecific respiratory diseases. In an analysis of the initial data from a prospective study of Boston policemen, Speizer and Ferris (*BP 61*) found that a higher percentage of men in three of four smoking categories who worked in areas of heavy traffic had chronic nonspecific respiratory disease compared with men who worked in the outskirts of Boston (figure 1).<sup>1</sup> In general, for each of the four traffic exposure

<sup>1</sup>Criteria for diagnosis of CNRD were those established by the British Medical Research Council Bronchitis Committee (1965).

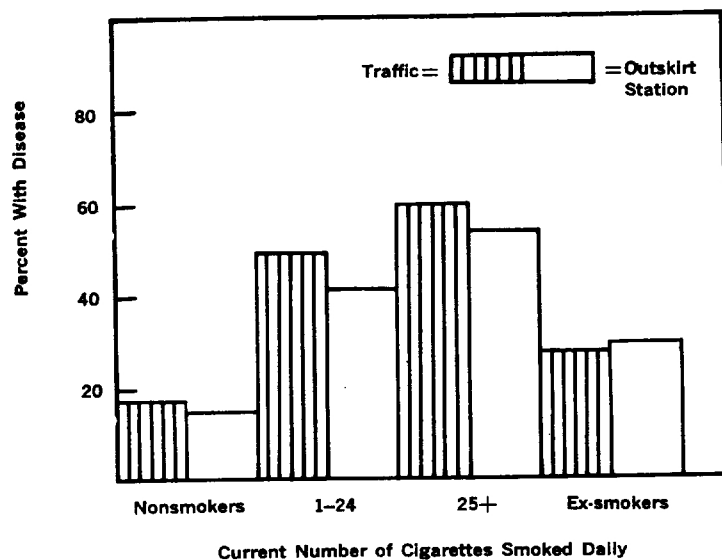


FIGURE 1.—Prevalence of chronic nonspecific respiratory disease by cigarette smoking habits and traffic exposure.

SOURCE: Speizer, F. E., Ferris, B. G., Jr. (*BP 61*).

categories, the prevalence of CNRD was greater among ex-smokers than nonsmokers, and greater among current cigarette smokers than among either ex-smokers or nonsmokers (table 2). Conversely, the prevalence of CNRD in current smokers appeared to be related to the number of years of traffic exposure; those men with few years of such exposure had approximately the same incidence as those who worked in the outskirts. In the analysis of this relatively homogenous group of men, it appears that "traffic pollution" and cigarette smoking may be acting in concert to increase the risk of developing chronic respiratory disease.

TABLE 2.—Prevalence of chronic nonspecific respiratory disease grouped by current cigarette categories and traffic exposure

	Total No. Men	Never in Traffic	In Traffic		
			1-10	11-20 yr	20+
Never smoked . . .	45*	11.5	11.1	25.0	16.7
Ex-smoker . . . . .	86	30.3	27.3	19.0	28.6
Current cigarette smoker . . . . .	137	49.2	44.1	57.7	64.3
Total . . . . .	268	36.1	35.2	39.2	39.0

\* Never smoked category includes 12 men who have smoked pipe and cigars.  
SOURCE: Speizer, F. E., Ferris, B. G., Jr. (BP 61).

These authors also measured pulmonary function in this cohort of policemen (BP 62) and found correlations between impairment of FEV<sub>1</sub> and lifetime cigarette smoking for all the men (P <.001). Statistically significant correlations between impairment of flow volume relationships at 50 and 25 percent lung volume and current cigarette consumption (P <.05 and <.001), and lifetime cigarette consumption (P <.01 and <.001) were found for the outskirt station officers, but not for the traffic officers, although the heavier smokers among them did demonstrate impairment of these parameters compared to the non-smokers and ex-smokers. The data also revealed that the heavier smokers with the longest exposure to traffic had the greatest impairment of flow-volume relationships at 50 percent (and 25 percent) vital capacity, again suggesting the synergistic action of air pollution and cigarette smoking in producing obstructive pulmonary disease.



### *The Relationship Between Cigarette Smoking and Small Airways Disease*

The role of small airways disease in the pathogenesis of COPD has come under close scrutiny in recent years. Results from several studies indicate that the resistance of airways less than 2 mm. internal diameter contributes little to the total measurable pulmonary resistance, and that considerable obstruction of these small airways may be present before changes in the total pulmonary resistance are recorded (*BP 41*). Several techniques have been developed to detect the presence of small airways disease, but some of these are technically difficult, expensive, and impractical for large-scale screening. The measurement of dynamic compliance was one of the first techniques used to demonstrate disease of the small airways (*BP 71*). Patients with small airways disease demonstrate frequency dependent decreases in dynamic compliance compared to controls. More recently, the measurement of closing volume (CV) has been used as a technically easier and less expensive method for the assessment of small airways function. The theoretical basis of these methods in the assessment of small airways disease is described in many recent publications (*BP 3, 4, 5, 10, 20, 23, 25, 28, 34, 36, 40, 41, 42, 43, 63, 66, 71*). It is currently unclear whether those subjects with evidence of small airways disease are particularly susceptible to the development of clinically identifiable forms of COPD.

McCarthy, et al. (*BP 40*) measured closing volumes in 112 subjects by the single-breath argon gas bolus method. Closing volume increased in a linear fashion with respect to age. Of the 66 nonsmokers, no subjects had closing volumes greater or less than 2 SDs from the mean normal values, whereas 26 of 39 cigarette smokers (7 smokers were excluded because of grossly abnormal ventilation distribution as measured by the argon technique) had closing volumes greater than 2 SDs above the mean (figure 2). This difference in closing volume was highly significant ( $P < .001$ ) and indicated a higher prevalence of small airways disease in the group of smokers. Of 14 smokers with abnormalities of standard pulmonary function tests, 13 were symptomatic and all but one had abnormal closing volumes. Of note was that of 17 asymptomatic smokers, 9 had abnormally high closing volumes. Although none of the smokers had sought medical attention, 29 of the 46 smokers had chronic bronchitis, and had, on the whole, higher closing volumes than the asymptomatic smokers.

In a separate publication, McCarthy and Craig (*BP 39*) reported that 15 percent of a group of 91 asymptomatic female smokers in Manitoba had abnormally high closing volumes (CV),

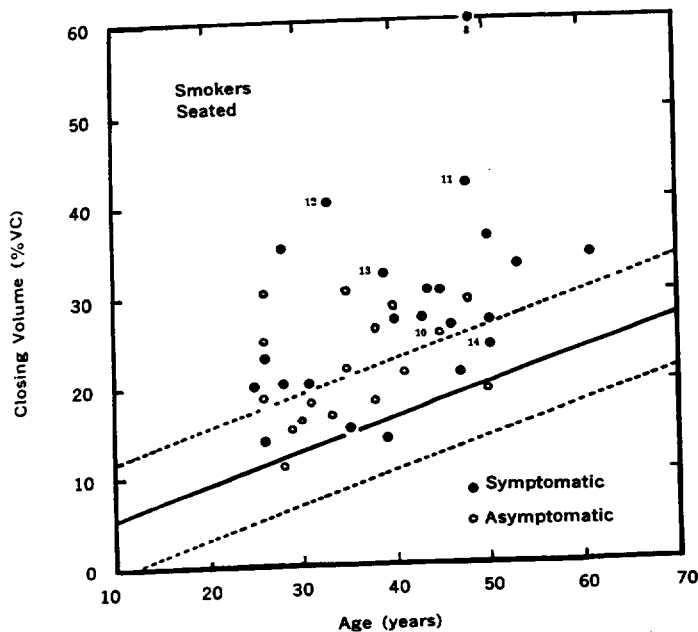


FIGURE 2.—Relationship between “closing volume” and age in 39 smokers. (Thirty-two smokers with normal conventional lung function data and seven smokers whose data are identified by numbers.) Average relationships  $\pm 2$  SD between “closing volume” and age in sixty-six nonsmokers are also shown. Solid circles indicate smokers who, according to the questionnaire used, had simple chronic bronchitis, and open circles indicate smokers who were asymptomatic. Note that in nine asymptomatic smokers the “closing volume” was above the normal limits.

SOURCE: McCarthy, D. S., et al. (BP 40).

in contrast to the 72 percent of 46 male smokers in London (BP 48) who had abnormally high closing volumes. None of the female nonsmokers had any CV abnormalities. The authors suggested that differences in pollution exposure of the London and Manitoba study groups might, in part, account for the differences in prevalence of the CV abnormalities.

In a study of pulmonary function of subjects voluntarily reporting to an emphysema screening center, Buist, et al. (BP 5) reported that 6 percent of the nonsmokers, 35 percent of the current cigarette smokers, and 23 percent of the ex-smokers had abnormal CV/VC ratios. In each decade from age 20 to 79, more smokers and ex-smokers had abnormal CV/VC ratios than nonsmokers (figure 3). The daily consumption of cigarettes was related to CV abnormalities in a dose-response relationship for men (figure 4). Among the women, those with a daily consumption of less than 10 cigarettes per day had significantly lower

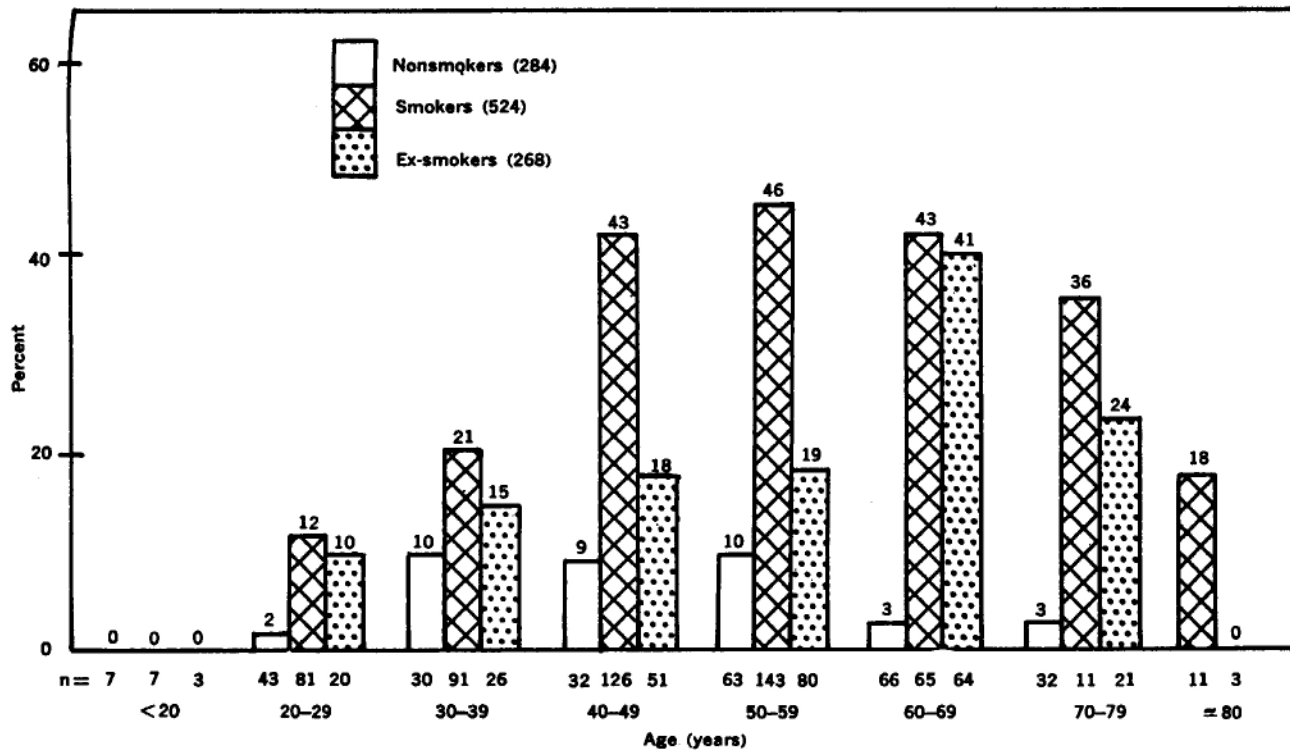


FIGURE 3.—Prevalence of abnormal closing volume/vital capacity ratios in non-smokers, cigarette smokers, and ex-smokers by age decades.

SOURCE: Buist, A. S., et al. (BP 5).

CV/VC ratios than those smoking more than this amount ( $P < .05$ ); but overall, no dose-response relationship was demonstrated (figure 5).

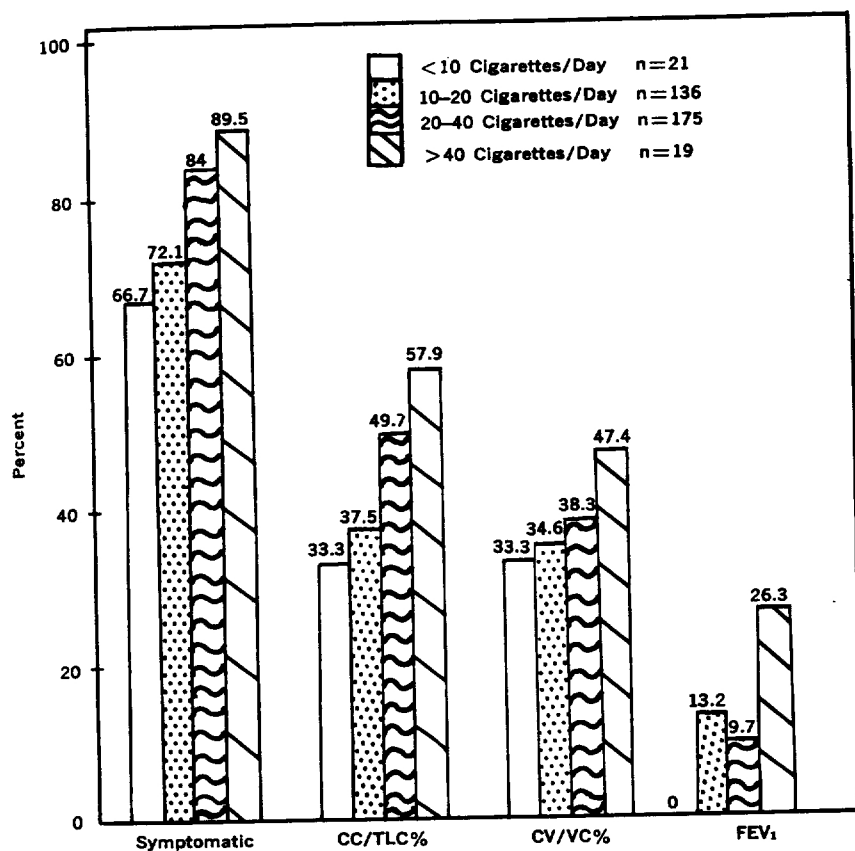


FIGURE 4.—Comparison of the prevalence of respiratory symptoms and pulmonary function abnormalities in male smokers according to their daily cigarette consumption.

CC —Closing capacity  
 TLC —Total lung capacity  
 CV —Closing volume  
 VC —Vital capacity  
 FEV<sub>1</sub> —One-second forced expiratory volume

SOURCE: Buist, A. S., et al. (BP 5).

### *The Interactions Between Cigarette Smoking and the Genetic Susceptibility to the Development of COPD*

Mittman, et al. (BP 47, 47, 49) reported on the interaction between cigarette smoking and the genetic susceptibility to development of chronic obstructive pulmonary disease (the alpha<sub>1</sub>-antitrypsin deficiency state). These authors described the

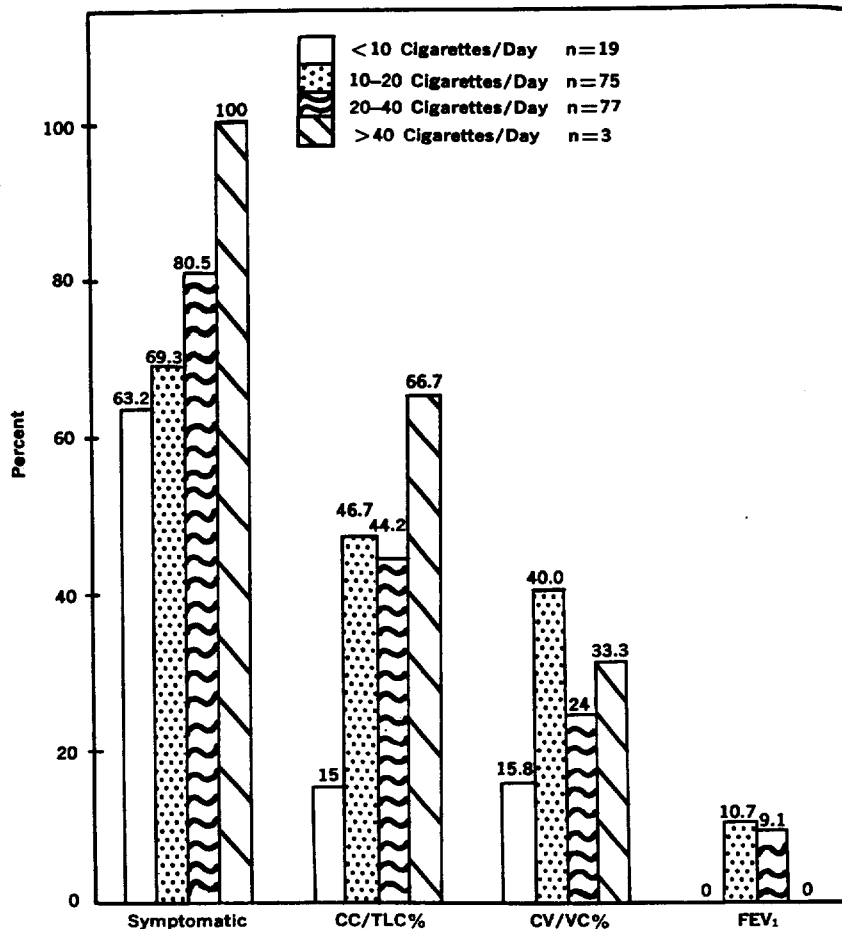


FIGURE 5.—Comparison of the prevalence of respiratory symptoms and pulmonary function abnormalities in female smokers according to their daily cigarette consumption.

CC —Closing capacity  
 TLC —Total lung capacity  
 CV —Closing volume  
 VC —Vital capacity  
 FEV<sub>1</sub> —One-second forced expiratory volume

SOURCE: Buist, A. S., et al. (BP 5).

polymorphic (multiple gene) system of protease inhibition (Pi) by alpha<sub>1</sub>-antitrypsin (AAT), and listed some of the partial and severe deficiency states of this enzyme system. In a series of 170 consecutive patients with a diagnosis of COPD admitted to the City of Hope Medical Center who had no previously known history of AAT deficiency, 40 patients (24 percent) demonstrated some type of AAT deficiency. This was a significantly higher

percentage than was found in a control group of the Norwegian population, which is known to have a high incidence of this enzyme deficiency ( $P < .001$ ). The lifetime cigarette consumption of the population of patients with emphysema who had an intermediate degree of AAT deficiency was significantly less than those emphysema patients with a normal phenotype ( $P_i^{MM}$ ) ( $P < .05$ ) (figure 6), suggesting a possible interaction between smoking and the genetic abnormality. The data imply that a greater degree of exposure to tobacco was required to produce

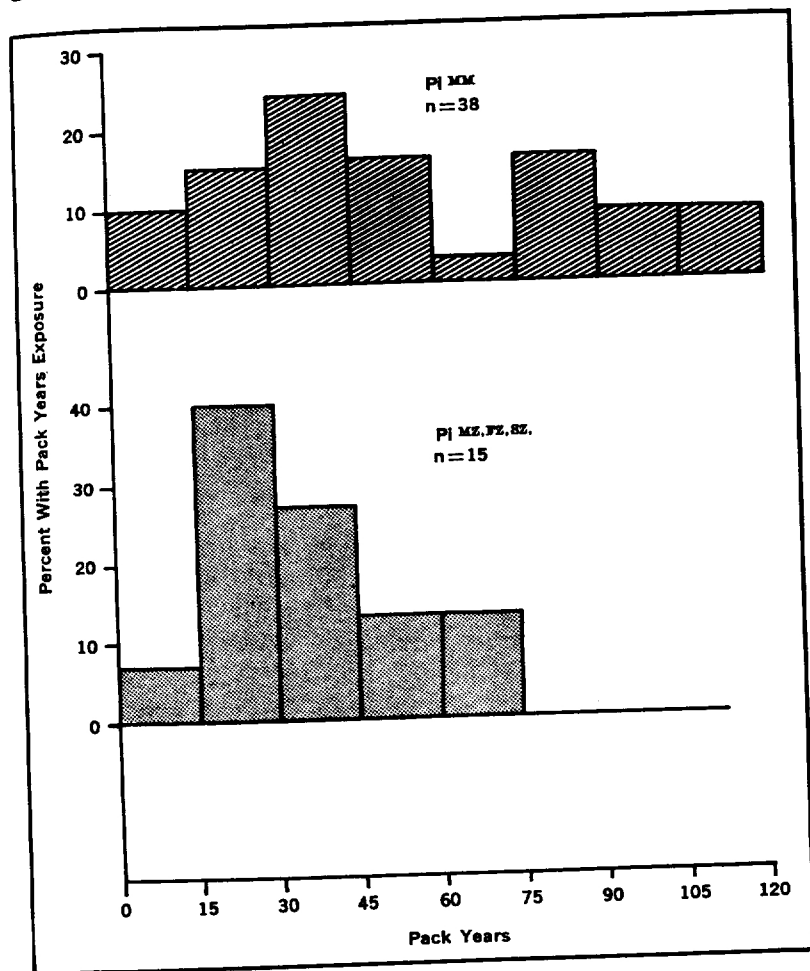


FIGURE 6.—The distribution of smoking histories in men with bronchitis and/or emphysema. Patients grouped by phenotype;  $P_i^{MM}$  patients above, those with intermediate AAT deficiency below. Each bar depicts the fraction of patients reporting smoking histories in the ranges shown.

SOURCE: Mittman, C., et al. (BP 48).

emphysema in those patients who did not have a genetic predisposition than in those with the genetic defect. The authors concluded that any degree of AAT deficiency makes an individual more susceptible to the effects of smoking. The same authors have also examined 144 people with partial AAT deficiencies who were apparently healthy and compared them with 100 controls matched for age, sex, and smoking history (BP 48). They found that 25 of the 62 smokers with partial AAT deficiency (40 percent) had abnormalities of pulmonary function tests suggestive of obstruction, while 7 of 47 smokers in the control group (15 percent) demonstrated such abnormalities. This difference was statistically significant ( $P < .05$ ).

Hutchison, et al. (BP 27) studied 28 patients with pulmonary emphysema, 8 of whom were homozygous deficient for alpha<sub>1</sub>-antitrypsin. Although the annual consumption of tobacco up to the age of onset of dyspnea was equal in the deficient and non-deficient group of patients, total lifetime tobacco consumption was significantly less among the AAT deficient patients than among the nondeficients ( $P < .01$ ). All 8 AAT deficient patients were smokers. Although there was no significant difference in the incidence or age of onset of chronic bronchitis between the two groups, the AAT deficient group of patients developed exertional dyspnea 12 years earlier than the nondeficients ( $P < .001$ ). These data suggest a synergistic effect of cigarette smoking on the development of pulmonary emphysema in those patients with homozygous deficiency of alpha<sub>1</sub>-antitrypsin.

Colley, et al. (BP 12) analyzed a cohort of 3,899 persons born in the last week of March 1946 in England, Scotland, and Wales and found that irrespective of a history of lower respiratory tract illness before the age of two, the smokers had a greater prevalence of symptoms of winter cough at age 20 than the nonsmokers (table 3). The authors argued that cigarette smoking, by age 20, is a far more important factor in the development of respiratory disease than is a history of lower respiratory tract illness. The results of this study are suggestive evidence against the hypothesis of a purely constitutional susceptibility to the development of respiratory diseases independent of tobacco exposure.

#### *The Effect of Smoking on the Development of Bullous Disease of the Lungs*

Stoloff and Victor (BP 64) reviewed 44,887 outpatient photofluorograms seen in the Philadelphia Central Mass X-ray Unit from 1969 to 1970, and found 59 men and one woman with bullous disease of the lung. Smoking information was available on

TABLE 3.—Prevalence (percent) of cough day or night in both sexes in winter by air pollution index, social class, cigarette smoking, and history of chest illness under two years of age.\* (Figures in parentheses are population.)

History of cigarette smoking	Chest illness under 2 years of age	Air pollution index			
		7-17 Social class		18-28 Social class	
		1 + 2	3 + 4	1 + 2	3 + 4
Never smoked	No chest illness . . . . .	4.7 (344)	5.7 (369)	4.7 (277)	6.6 (212)
	One or more chest illnesses . . . . .	12.3 (57)	8.3 (108)	8.3 (84)	10.8 (102)
Present smoker	No chest illness . . . . .	11.2 (214)	12.6 (325)	14.1 (192)	15.7 (261)
	One or more chest illnesses . . . . .	16.4 (55)	11.8 (102)	12.3 (73)	22.2 (144)

\*Excluding 980 persons—that is, ex-smokers and those whose history of cigarette smoking, social class, air pollution index, chest illness under 2 years of age, and history of cough day or night not known.

SOURCE: Colley, J. R. T., et al. (BP 12).

51 of the men. There were no nonsmokers among the 51 cases ( $P < .001$ ). In nonwhite and white men under age 45 and in nonwhites greater than 45 years old, the rates of this disease increased for each progressively higher level of daily cigarette consumption (table 4). When men without known possible or probable occupational hazards were studied, dose-response relationships were again demonstrated in the nonwhite population, inclusive of all age groups (table 5). The absence of dose-response relations in whites older than 45 may be at least partially explained by the small numbers of cases of bullous disease of the lung found in whites (19 of the 51 cases). The authors stated that the data "are consistent with the hypothesis that cigarette smoke is capable of causing alveolar septal rupture . . ." and, hence, bullous disease of the lung.

TABLE 4.—Estimated rates of bullous disease of the lung per 1,000 men by age, race, and cigarette smoking habits.

Race, Sex Age, yr	Nonsmoker	<1 Pack/Day	1 Pack+/Day
WM			
25-44 . . . . .	0	0	1.0
45+ . . . . .	0	4.5	2.9
NWM			
25+ . . . . .	0	4.3	9.9
45+ . . . . .	0	4.1	13.0

SOURCE: Stoloff, I. L., Victor, S. B. (BP 64).



TABLE 5.—*Estimated rates of bullous disease of the lung per 1,000 men with no demonstrable occupational hazard (class 1).*

Race, Sex Age, yr	Nonsmoker	<1 Pack/Day	1 Pack+/Day
WM			
25-44 -----	0	0	0
45+ -----	0	4.0	2.2
NWM			
25-44 -----	0	2.0	5.4
45+ -----	0	4.6	7.7
Total -----	0	5.2	4.9

SOURCE: Stoloff, I. L., Victor, S. B. (BP 64).

#### *Smoking and Post-Operative Complications*

Laszlo, et al. (BP 35) studied the incidence of post-operative pulmonary complications in 52 bronchitic and 88 nonbronchitic patients undergoing elective surgery in London. They found that a significantly higher percentage of current nonbronchitic smokers (53 percent) developed post-operative pulmonary complications than nonbronchitic nonsmokers (22 percent) ( $P < .02$ ). In patients with no history of chronic bronchitis, there was a dose-response gradient of post-operative bronchitis and/or pneumonia from nonsmokers through ex-, light, and heavy smokers. The presence of bronchitis did not seem to influence the effects of smoking; the bronchitic and nonbronchitic smokers had an equal incidence of pulmonary complications. Of the six cases of severe post-operative bronchitis, five occurred in smokers. The authors noted that each of the three patients who developed severe purulent bronchitis after minor surgery smoked more than one pack of cigarettes per day.

#### *The Influence of Cigarette Smoking on the Development of Pulmonary Disease Associated with Rheumatoid Arthritis*

Frank, et al. (BP 17) investigated 14 men and 27 women with classical rheumatoid arthritis and evaluated the presence or absence of pulmonary dysfunction in this group. They reported the presence of pulmonary function abnormalities in 57 percent of the men and 33 percent of the women. The men with abnormal pulmonary function tests (spirometry and CO diffusion) had a higher mean lifetime consumption of cigarettes than men with normal pulmonary function tests ( $P < .05$ ); however, the mean age of the abnormal group was 5 years greater than that of the normal group. The women with abnormal values of pulmonary

function tests smoked more than those with normal values (14.44 vs. 9.72 pack years), but the difference was not statistically significant. The group of women with abnormal values was also slightly older than the normal group (by 1.12 years).

### Occupational Diseases and Smoking

#### Byssinosis

Kilburn, et al. (*BP 32*) reported on the prevalence of chronic bronchitis in wool and cotton mill workers in North Carolina. These investigators found that in women the combination of cigarette smoking and cotton dust exposure was associated with a marked increase in the prevalence of chronic bronchitis (figure 7). Of the nonsmoking nonexposed employees, less than 1 percent had chronic bronchitis. Cotton dust exposure and cigarette smok-

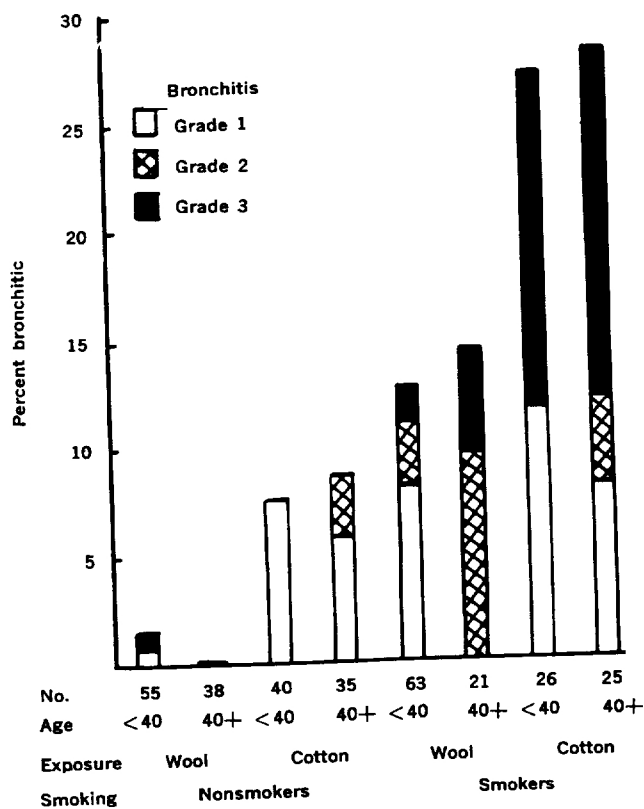


FIGURE 7.—Chronic bronchitis in female wool and cotton textile workers.

SOURCE: Kilburn, K. H., et al. (*BP 32*).

ing alone were associated with prevalence rates of 7 percent and 13 percent, respectively. Both exposures in combination resulted in a prevalence rate for chronic bronchitis of 27 percent. For men, a synergistic effect was demonstrated (figure 8), but it was not as striking as that for women. The authors suggested that the differences in prevalence of chronic bronchitis between men and women, and the differences in the effects of the two noxious exposures in combination may have been due to the fact that men were more heavily exposed to both cotton dust and cigarette smoke than women.

In a cross-sectional survey of 1,140 cotton workers in England, Fox, et al. (*BP 16*) found by regression analysis, that for each level of dust exposure (mg. yrs./m.<sup>3</sup>) smokers and ex-smokers had lower FEV<sub>1</sub> observed/predicted percent than nonsmokers. The differences in the slopes of these lines were not significant (figure

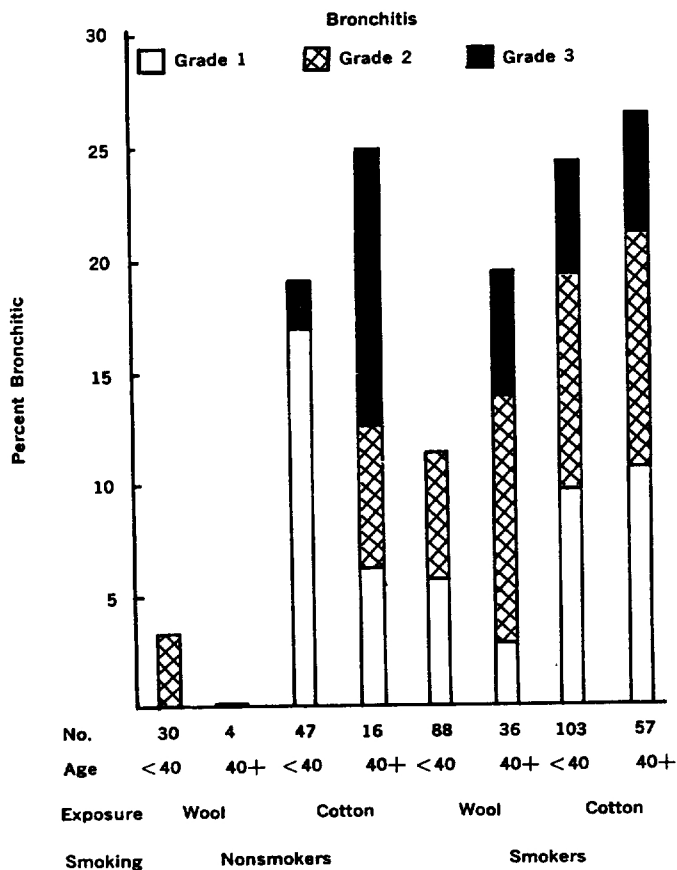
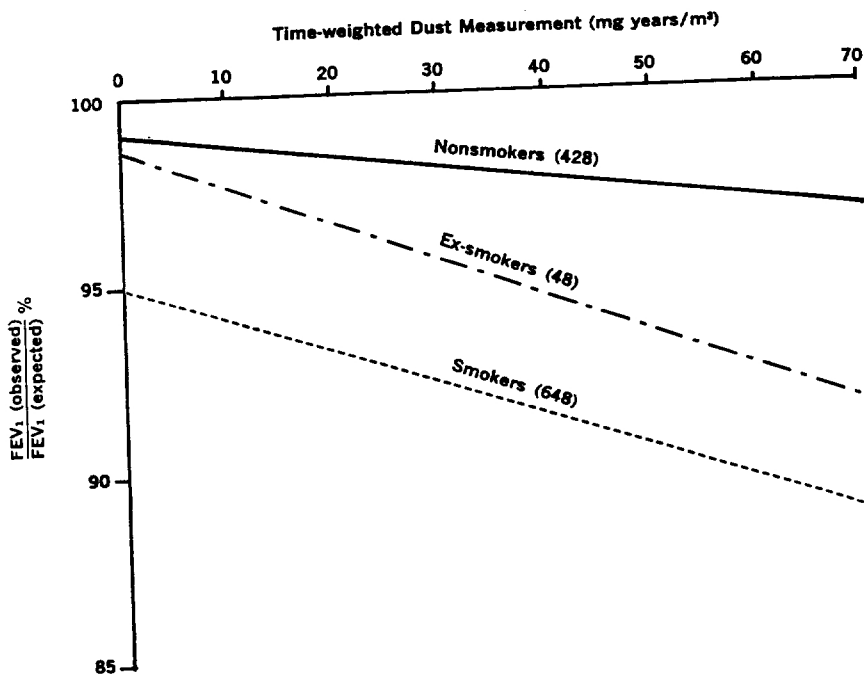


FIGURE 8.—Chronic bronchitis in male wool and cotton textile workers.

SOURCE: Kilburn, K. H., et al. (*BP 32*).

9). The authors also reported that the percentage of smokers with byssinosis was higher than that for nonsmokers at each level of exposure, the slopes of the lines being significantly different ( $P < .001$ ) (figure 10).



'Nonsmokers':

$$\frac{FEV_{1.0} \text{ (observed)}}{FEV_{1.0} \text{ (expected)}} \% = 99.00 - 0.035 \times (TWDM); r = -0.08$$

'Smokers':

$$\frac{FEV_{1.0} \text{ (observed)}}{FEV_{1.0} \text{ (expected)}} \% = 94.68 - 0.083 \times (TWDM); r = -0.13$$

FIGURE 9.—Effect of smoking on pulmonary ventilation ( $FEV_{1.0}$ ) at different levels of time-weighted dust exposure.

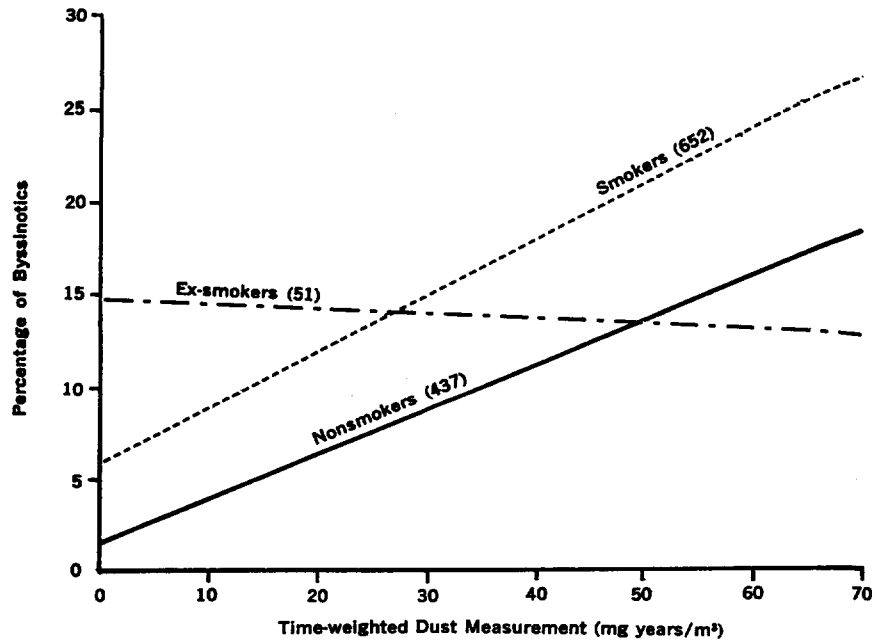
SOURCE: Fox, A. J., et al. (*BP 16*).

### Asbestosis

Chew, et al. (*BP 9*) examined 112 asbestos workers in Singapore and found only slight differences in mean  $FEV_{1.0}$ s between smokers and nonsmokers (2.73 L and 2.79 L, respectively).

### Chronic Bronchitis and Pulmonary Symptoms in Cement and Rubber Industry Workers

In a cross-sectional study of 847 cement workers in Yugoslavia, Kalacic (*BP 29, 30*) found that nonsmokers had a higher prevalence of cough, sputum production, exertional dyspnea, and



'Nonsmokers':  
 $\% = 1.57 + 0.23 \times (\text{TWDM})$ ;  $r = 0.27$

'Smokers':  
 $\% = 5.76 + 0.30 \times (\text{TWDM})$ ;  $r = 0.25$

FIGURE 10.—Effect of smoking on prevalence of byssinosis at different time-weighted dust exposure levels.

SOURCE: Fox, A. J., et al. (BP 16).

chronic bronchitis than controls with other occupations. Within the group of cement workers, cigarette smokers had higher prevalence rates of cough, sputum production, exertional dyspnea, wheezing, and chronic bronchitis than nonsmokers regardless of the number of years of exposure in the cement plants. No significant differences in FVC or FEV% were observed between cigarette smoking and nonsmoking cement workers.

Osman, et al. (BP 51) studied 230 rubber industry employees in Egypt and found a higher prevalence of upper respiratory tract irritation, acute bronchitis, and chronic bronchitis in smokers compared to nonsmokers (NS). There was a lower prevalence of these three conditions among control smokers compared with smokers exposed to these industrial fumes, thereby suggesting a synergistic action of cigarette consumption and exposure to rubber industry fumes.

## AUTOPSY STUDIES

### *The Effect of Smoking on the Prematurity of Development and Severity of COPD*

Spain, et al. (BP 60) evaluated the degree of emphysema in whole lung mounts of 134 victims of accidents, suicide, homicide, or sudden coronary death autopsied at the office of the Medical Examiner of Westchester County (85 men and 49 women). Degree of emphysema was graded from 0 to 100. In men, 3 of 30 nonsmokers had grades of 20 or higher (10 percent), while 16 of 41 heavy smokers had grades of 20 or higher (39 percent). This difference was significant ( $P < .01$ ). The highest grade which the nonsmokers reached was 20, whereas several of the heavy smokers reached grades of 50 (precise data not given). The mean ages of the nonsmokers, light smokers, and heavy smokers with grades 20 or greater were 66, 62, and 52, respectively. The mean grade of emphysema in all the heavy smokers was 14, compared to 11 in the lighter smokers and 8 in the nonsmokers. Among 21 nonsmoking women, there were no cases of grade 20 or greater, while in the heavy smokers 5 of 22 cases had grade 20 or greater. The mean age of this group of smokers was 40. For the women, as in the men, the mean grade of emphysema rose with the intensity of smoking. The authors attributed the differences in degrees of emphysema solely to smoking.

### *Smoking and Mucous Gland Abnormalities*

In an autopsy series in Glasgow of 149 men and women with known smoking histories, Scott (BP 57) studied the degree of mucous gland hypertrophy using the Reid index and point-counting technique. He found that the mean Reid index was significantly greater in smokers than nonsmokers ( $P < .01$ ) and that fewer smokers had normal Reid indices than nonsmokers ( $P = .02$ ). Although more smokers had an abnormally high Reid index compared to nonsmokers, the difference was not statistically significant. In this autopsy series, the Reid index was found to be higher in young subjects; also men were noted to have a significantly higher index than women ( $P < .05$ ).

### *Abnormalities of the Small Airways*

Matsuba and Thurlbeck (BP 44), in a study of postmortem lung specimens, found that in patients with chronic bronchitis without emphysema who died of nonrespiratory causes, there

was significant narrowing of small airways compared to patients without either chronic bronchitis or emphysema, as measured by the smaller average diameter of the small airways ( $P < .001$ ). These patients had an excess of airways with 0.2 to 0.6 mm. internal diameter and a deficit of airways with an internal diameter of 0.6 to 1.8 mm. (figure 11). In addition, these workers observed more mucus in the airways of the patients with chronic bronchitis without emphysema than in those patients without either disease. The authors concluded that both small airway narrowing and mucus plugging constitute the major morphologic lesions corresponding to the functional abnormalities of small airways seen in patients with chronic bronchitis.

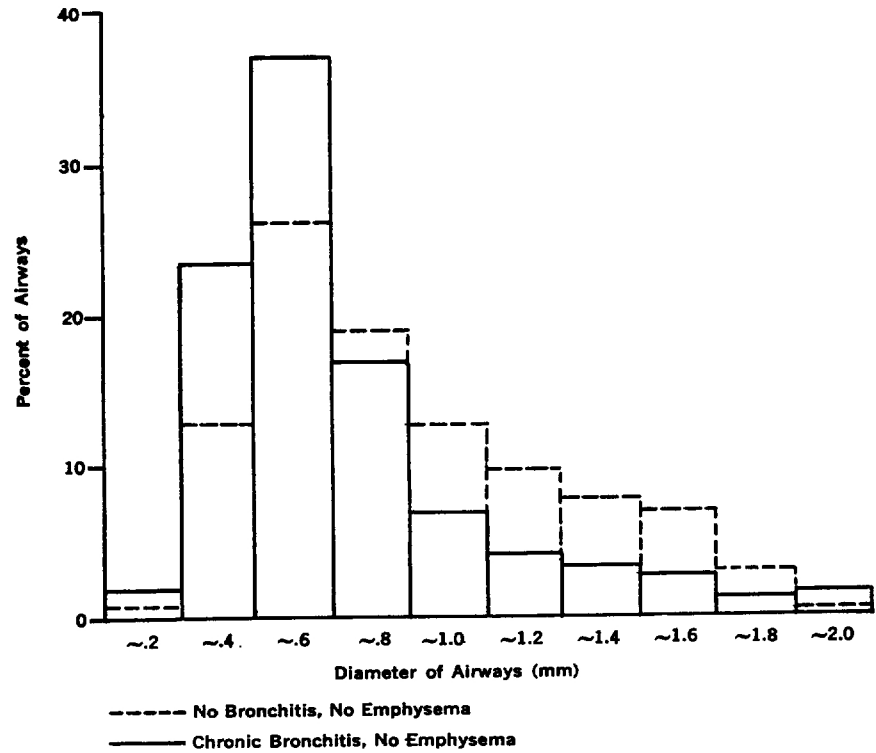


FIGURE 11.—A frequency distribution curve of the internal diameters of the small airways in an autopsy population of nonemphysematous patients with and without histories of chronic bronchitis.

SOURCE: Matsuba, K., Thurlbeck, W. M. (BP 44).

## EXPERIMENTAL STUDIES

### *Studies in Humans*

Paterson, et al. (BP 52) measured pulmonary function in a group of 16 nonsmokers and 10 heavy cigarette smokers before and after exercise. No significant differences in FVC, FEV<sub>1</sub>, MMEFR, and FRC were observed between these two groups before exercise. However, after exercise, the smokers exhibited a greater drop in MMEFR, FEV<sub>1</sub>, and specific airways conductance than the nonsmokers, thus demonstrating that post-exercise airways narrowing was greater in the smokers. The nonsmokers demonstrated a greater improvement in all these parameters measured after exercise following use of disodium chromoglycate (an anti-bronchoconstrictive agent) than the smokers. The authors suggested that the increase in airways resistance in nonsmokers was mostly due to bronchoconstriction; that seen in smokers was thought to be a combination of bronchoconstriction, mucosal edema, and accumulation of secretory debris.

Using simultaneous helium bolus and nitrogen dilution techniques on 9 subjects, Linn and Hackney (BP 38) showed that, with the He method, none of 4 nonsmokers had mean CV/VC % greater than 15.9, whereas both the current cigarette smokers and the one ex-smoker had CV/VC % greater than 21.3. The one pipe smoker had a ratio of 18.9. With the nitrogen dilution technique, the same pattern of abnormalities of the CV/VC ratio in this group of subjects was demonstrated. The highest CV/VC % among the nonsmokers was 17.4, and the lowest among the current, ex-, and pipe smokers was 18.0.

Reintjes, et al. (BP 54) studied the acute effects of smoking one cigarette on large airway resistance in a group of 30 young healthy male volunteers (15 smokers and 15 non and ex-smokers), and found that immediately after the smoking of one nonfilter cigarette there was a significant increase in mean airway resistance for both smokers and nonsmokers ( $P < .001$ ). The FEV<sub>1</sub> % did not vary after the smoking of the cigarette in either group of volunteers.

Da Silva and Hamosh (BP 14) reported on pulmonary function tests performed on 21 volunteers before and after smoking one nonfilter cigarette, and found that total airway resistance (Raw) was significantly increased ( $P < .001$ ) and MEF<sub>50%</sub> was significantly decreased after smoking ( $P < .001$ ). Other measurements, including those used to assess small airways function, showed no significant changes from the control to the post-smoking states.

Stone, et al. (BP 65) conducted experiments on 19 volunteers,



4 of whom had chronic bronchitis. There were 11 cigarette smokers and 8 nonsmokers. These authors found that the infusion of isoproterenol increased specific airway conductance (SGaw) equally in smokers, nonsmokers, and patients with chronic bronchitis. Likewise, infusion of propranolol decreased SGaw equally in all these groups of subjects. Alpha-adrenergic stimulation and blockade had no effect on SGaw in any of the experimental groups.

In an experimental study evaluating pulmonary clearance in 79 elderly subjects, Thomson and Pavia (*BP 67*), utilizing  $Tc^{99m}$ -labeled polystyrene particles of  $5\mu\text{m}$ ., found no statistically significant difference in pulmonary (mucociliary) clearance of these particles between smokers and nonsmokers with and without evidence of obstructive and restrictive pulmonary disease. The volume of inhaled particles was controlled in this group of experiments. There was a slight diminution in mucociliary clearance of the healthy smokers compared to the nonsmokers. The group of subjects with impaired pulmonary function had higher clearance rates than the normals, probably owing to the greater deposition of particles nearer the mouth. Among the subjects with subnormal pulmonary function, smokers had slower clearance rates from 1 to 5 hours after inhalation of the particles, but these differences were not statistically significant (figures 12 and

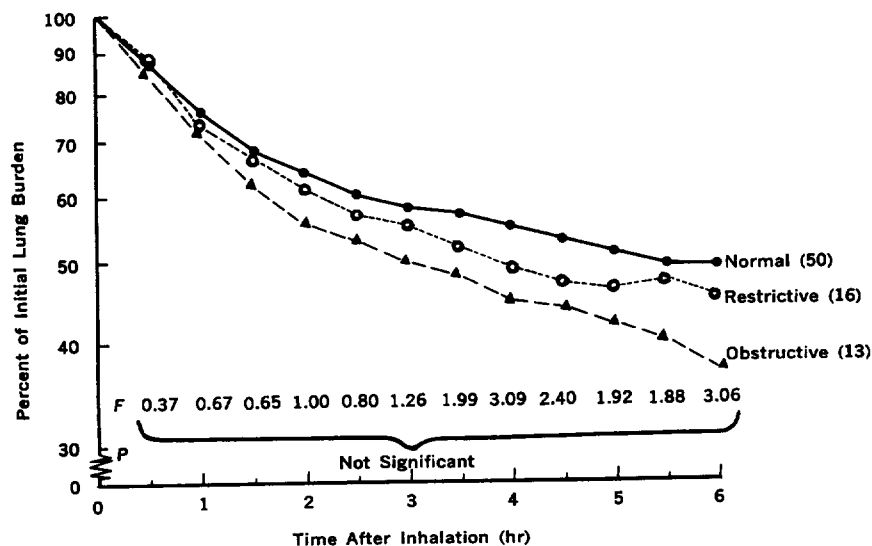


FIGURE 12.—Mean clearance curves for normal subjects, subjects with airway obstruction, and restrictive impairment of the lungs. F=Snedecor's F; the value required for significance here at the 5 percent level is 3.11.

SOURCE: Thomson, M. L., Pavia, D. (*BP 67*).