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6. NON-NEOPLASTIC BRONCHOPULMONARY DISEASES.

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Introduction

The chronic non-neoplastic bronchopulmonary diseases pose a major worldwide health challenge. The chronic obstructive lung diseases (COLD), chronic bronchitis, and emphysema comprise the majority of these illnesses and rank second only to coronary artery disease as a cause of Social Security-compensated disability (*73*). Previous reports on the health consequences of smoking (*141-149*) have reviewed the relationship between smoking and these disorders. They are summarized below.

Cigarette smoking is the most important cause of COLD. Cigarette smokers have higher mortality rates from chronic bronchitis and emphysema, an increased prevalence of respiratory symptoms, and diminished performance on pulmonary function testing compared to nonsmokers. These differences become more marked as the number of cigarettes smoked increases. Cigarette smokers without respiratory symptoms have evidence of small airway dysfunction more frequently than do nonsmokers. The relationship between cigarette smoking and COLD has been demonstrated in many different national groups and is more striking in men than in women. Pipe and cigar smokers have higher morbidity and mortality rates from COLD than do nonsmokers but are at lower risk for COLD than are cigarette smokers.

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

Cigarette smokers experience an increased risk for respiratory problems other than COLD. They experience more frequent respiratory tract infections. In response to mild viral respiratory illness cigarette smokers develop abnormal but reversible changes in certain pulmonary function tests. Cigarette smokers have more protracted respiratory symptoms following mild viral illness and are at greater risk for developing postoperative respiratory complications and possibly spontaneous pneumothorax as compared to nonsmokers.

Cigarette smokers who die from diseases other than COLD have anatomic evidence of COLD more frequently than do nonsmokers. Autopsy studies have shown a dose-response relationship between cigarette smoking and the microscopic changes of COLD. Histologic

evidence of bronchiolitis may be more common in cigarette smokers than in nonsmokers.

Increased susceptibility to and premature development of emphysema occurs in individuals with severe genetically determined deficiencies of an antiprotease, alpha-1-antitrypsin. There is some evidence that smoking hastens the development of COLD in such individuals but it is unknown whether smoking places subjects with less severe types of deficiency at a greater risk for developing emphysema.

Experimental animal and human data have demonstrated that inhalation of cigarette smoke impairs pulmonary clearance, ciliary function, and alveolar macrophage activity. Pathological changes of emphysema and fibrosis have been noted in dogs trained to inhale cigarette smoke through a tracheostoma; these changes follow a dose-response relationship.

Many recent studies confirm and extend these observations. In addition, there have been considerable advances in our understanding of the relationship of smoking to the natural history and pathogenesis of these disorders. In the following discussion, these relationships will be examined in subjects of all ages as well as in animal models. Evidence will be presented documenting the effects of smoking on the integrity of the bronchopulmonary system, and the proposed pathogenetic mechanisms will be reviewed. Finally, a number of other risk factors which may interact with smoking in producing lung damage will be scrutinized.

Definitions

The terms chronic bronchitis and emphysema have been used diagnostically for many years, but the criteria on which each diagnosis rests have only recently been stated clearly (*54*). Physicians often use these terms interchangeably to describe a patient with chronic airflow obstruction. The confusion between chronic bronchitis and emphysema has been compounded further by the manner in which they have been defined by various scientific societies, in different studies, and in different nations (*55*).

Clinically pure forms of chronic bronchitis and emphysema are the exceptions rather than the rule. They are often difficult to distinguish from each other in patients with chronic airflow obstruction because (1) some degree of each may coexist in the same patient; (2) both disorders are usually characterized by expiratory flow obstruction; and (3) patients with either disorder frequently present the same symptom: dyspnea on exertion. Consequently the clinician often labels the patients with chronic expiratory flow obstruction as having COLD.

The most widely accepted definitions in the United States are those of a joint committee of the American College of Chest Physicians and the American Thoracic Society (*4*):

Bronchitis: A non-neoplastic disorder of structure or function of the bronchi resulting from infectious or noninfectious irritation. The term bronchitis should be modified by appropriate words or phrases to indicate its etiology, its chronicity, the presence of associated airways dysfunction, or type of anatomic change. The term chronic bronchitis, when unqualified, refers to a condition associated with prolonged exposure to nonspecific bronchial irritants and accompanied by mucous hypersecretion and certain structural alterations in the bronchi. Anatomic changes may include hypertrophy of the mucous secreting apparatus and epithelial metaplasia, as well as more classic evidence of inflammation. In epidemiologic studies, the presence of cough or sputum production on most days for at least three months of the year has sometimes been accepted as a criterion for the diagnosis.

Pulmonary Emphysema: An abnormal enlargement of the air spaces distal to the terminal nonrespiratory bronchiole, accompanied by destructive changes of the alveolar walls. The term emphysema may be modified by words or phrases to indicate its etiology, its anatomic subtype, or any associated airways dysfunction.

COLD: This term refers to diseases of uncertain etiology characterized by persistent slowing of airflow during forced expiration. It is recommended that a more specific term, such as chronic obstructive bronchitis or chronic obstructive emphysema, be used whenever possible.

It should be noted that these definitions may have serious inadequacies (*138*), particularly when applied to longitudinal studies assessing the natural history of COLD (*56*). In the following discussion, cognizance is taken of these limitations.

Smoking and Respiratory Mortality

Numerous retrospective and prospective studies have shown a greatly increased mortality from COLD among smokers as compared to nonsmokers. Results from the major prospective studies relating smoking to mortality from COLD are presented in the Chapter on Mortality and reproduced in Table 1. These studies represent over 13 million patient years of observation and approximately 270,000 deaths from all causes. The number of deaths related to COLD is probably underestimated since some of the deaths attributed to pneumonia or myocardial disease may have been due to complications of COLD. In addition, these mortality figures do not include a sizeable number of individuals for whom COLD may have been a major contributory cause of death. For example, it is not uncommon for individuals to have COLD and lung cancer simultaneously.

TABLE 1.—COLD mortality ratios in six prospective studies

	British Doctors	Men in 25 States 45–64	Men in 25 States 65–79	U.S. Veterans	Canadian Veterans	Men in 9 States	California Occupations
Emphysema and/or bronchitis	24.7	—	—	10.08	—	2.30	4.3
Emphysema without bronchitis	—	6.55	11.41	14.17	7.7	—	—
Bronchitis	—	—	—	4.49	11.3	—	—

SOURCE: See Table 41 of Chapter 2. Mortality.

TABLE 2.—Smoking habit when last asked and death from chronic bronchitis and emphysema

No. of deaths	Annual death rate per 100,000 men, standardized for age							X^2	
	Non-smokers	Current or ex-smoker	Ex-smoker	Current smokers any tobacco	Current smokers any tobacco (g/day)			Nonsmokers vs other	Trend (dose-response)
					1–14	15–24	25		
254	3	48	44	50	38	50	88	25.58*	47.23*

*$p<0.001$
SOURCE: Doll, R. (42)

Doll and Peto (42) have recently reported their 20-year followup of 34,440 British male physicians. The data, presented in Table 2, demonstrate an increased mortality ratio in all current smokers and a dose-response relationship to the number of cigarettes smoked. They also found a 1.5-fold higher death rate in smokers who inhaled as compared to smokers who did not inhale. The mortality in individuals who quit smoking increased during the fifth to ninth year but thereafter fell sharply (Table 3). The authors suggest that the men who died during this period from lung disease stopped smoking because they had irreversible disabling disease such that a few more years of normal functional decline resulted in their death.

Smoking and the Natural History of COLD

The adverse effects on the lungs of smoking have been demonstrated in very young, working age, and elderly populations. Although there is a clear relationship between the presence of COLD and a prior history of smoking, only a small proportion of smokers are severely disabled and die from COLD. Therefore, many investigators have scrutinized the natural history of smoking-related lung changes in an attempt to identify smokers at increased risk of developing COLD. Three methods have been employed: clinical, physiological, and pathological.

TABLE 3.—Mortality from chronic bronchitis, emphysema, and pulmonary heart disease in ex-cigarette smokers compared with mortality in lifelong nonsmokers

No. of deaths divided by number expected in lifelong nonsmokers. Years since stopped smoking					No. of deaths in lifelong nonsmokers
0*	5	5–9	10–14	>15	
35.6	34.2	47.7	7.3	8.1	2

*Current smokers are described as having stopped 0 years ago.
SOURCE: Doll, R. (*42*)

Clinical data are more readily obtained than pathological or physiological data. However, the relationship of early respiratory symptoms to subsequent development of COLD is unclear. Physiological data can be quite specific (disease versus no disease), but, until recently, functional tests were unable to detect the early effects of smoking on lung function. Tests of small airway function may identify such a stage, i.e., airways abnormality prior to symptoms and before airflow reduction can be measured by conventional spirometry. However, longitudinal studies demonstrating that individuals with abnormal tests of small airway function are at greater risk for COLD are unavailable. Pathological data are the most specific and sensitive parameters relating smoking to lung changes but generally are inaccessible during life. A few studies are now available relating lung pathology to smoking in young individuals.

Youthful Smoking and Respiratory Morbidity

A number of recent studies have established a higher prevalence of respiratory symptoms in adolescent, teenage, and young adult smokers as compared to nonsmokers. Bewley and Bland (*13*) examined the relationships between smoking and the prevalence of respiratory symptoms in 14,033 children aged 10 to 12-1/2 in two separate areas of the United Kingdom. In this questionnaire survey, 4.7 percent acknowledged smoking at least one cigarette per week ("smoker") and about 1 percent of the boys smoked more than one cigarette per day. Male smokers, who outnumbered female smokers threefold, reported more morning cough (17.4 to 6.4 percent), cough during the day or night (41.4 to 20.5 percent), and cough of 3 months duration (14.5 to 4.8 percent) than their nonsmoking classmates. These relationships were similar to those in females although based on smaller numbers of smokers.

Rush (*123*), in a survey of 12,595 high school students in Rochester, New York, found that reported respiratory symptoms (regular cough, phlegm production, and/or wheezing) strongly correlated with smok-

ing. In a re-survey (*122*) done a year later of a segment of this population (2,749 white students), he found a similar rate of smoking for both girls and boys (30.2 and 32.4 percent, respectively). Cessation of smoking resulted in only partial reversibility of respiratory symptoms within this time interval.

Kiernan, et al. (*80*) surveyed the respiratory symptoms and smoking habits of a British population of 25-year-olds followed since birth and previously examined at age 20. Current smokers had a 6.8 percent crude prevalence rate of cough, day or night, as compared to a 3.1 percent rate for those who had never smoked. Individuals who were smokers at age 20 and 25 had an 11.6 percent prevalence of symptoms, and individuals who had smoked at 20 but were ex-smokers at 25 had a 3.9 percent prevalence of symptoms.

In summary, these clinical data suggest that cigarette smoking even in these young age groups produces pulmonary symptoms. Cessation of smoking leads to at least partial resolution of symptoms. Pulmonary function (*127*) and histologic (*112*) abnormalities also have been observed in young smokers, confirming clinical suspicions of lung injury in this group.

Early Stages of Respiratory Dysfunction

In an effort to identify individuals at high risk for developing COLD, a number of investigators have examined the relationship of smoking to physiological changes not detectable by standard spirometry. Individuals with functional abnormalities in tests of small airway function may be such a high risk group. Anthonisen, et al. (*5*) observed abnormalities of regional gas exchange, as determined by inhaling ^{133}Xe, in a group of individuals with mild chronic bronchitis and well preserved lung function as measured spirometrically. The authors attributed these abnormalities to peripheral airway disease and suggested that the functionally important lesions in chronic bronchitis might be in the peripheral airways. Other investigators showed that airways less than 2 mm contributed little to the total pulmonary resistance in patients with normal lungs but were the main site of airflow obstructions in patients with chronic bronchitis and emphysema (*19*, *69*, *97*). These earlier reports led to the development of tests believed to measure small airway function.

A decrease in the ratio of dynamic to static compliance with increases in respiratory frequency was demonstrated by Woolcock, et al. (*160*) in a group of bronchitics with normal standard spirometry. This "frequency dependence of compliance" test appears to be a sensitive indicator of small airway dysfunction but it is cumbersome to perform and available in few laboratories.

The measurement of closing volume and of the slope of the alveolar plateau on a single breath nitrogen washout (*6*) are technically easier to record and have been widely applied in epidemiological surveys. The

closing volume is the lung volume at which the dependent lung zones stop contributing to the expired air flow and when expressed as a percent of total lung capacity is called closing capacity. The slope of the alveolar plateau is usually measured as the change in nitrogen concentration per liter. The precise physiologic event that this test measures is unclear, but it is thought to reflect the degree of homogeneity of ventilation and, when abnormal, to be a sensitive indicator of small airways dysfunction.

Maximum expiratory flow rates at 25 and 50 percent of vital capacity (*59*) measure flow at lung volumes where the resistance of the small airways comprises a larger proportion of the total resistance. Such measurements appear to be of particular value in assessing small airway function when performed before and after inhalation of an 80 percent helium and 20 percent oxygen mixture (*72*). Changes in both maximal flow rates and changes in the lung volume at which the same flow is achieved (volume of isoflow) indicate small airways dysfunction.

Several reports have demonstrated a higher prevalence of abnormalities in these tests of small airways function in smokers as compared to nonsmokers. However, as can be seen in Table 4, studies show wide variability in the percent of smokers demonstrating an abnormal test. Such variability most likely reflects testing of different populations (random vs. selected), the use of different standards of normalcy, and the application of different techniques for the same test. As can be seen from Table 4, a dose-response relationship often exists between the intensity of smoking and the percent of smokers with abnormal tests.

In a recent study, Dosman, et al. (*43*) examined the relationship between respiratory symptoms and tests of small airway function in clinically healthy cigarette smokers. They found that the presence of individual symptoms (cough, sputum, wheezing, and shortness of breath) correlated poorly or not at all with measured values for dynamic lung compliance, closing volume, closing capacity, slope of the alveolar plateau, and helium-oxygen flow curves. Moreover, 53 percent of their smoking population conformed to the American Thoracic Society criteria for a diagnosis of chronic bronchitis although all had a forced expiratory volume $FEV_1 \geq$ 70 percent. They suggested that symptoms could not be used to detect smokers who have abnormalities of small airway function.

The insensitivity of certain respiratory symptoms in the adult as a predictor of future development of COLD has been emphasized by Fletcher, et al. (*57*) in a prospective study of 792 men, aged 30 to 59, who were followed for 8 years. They found that smoking was strongly related to the presence of symptoms (mucous hypersecretion) and to the development of airflow obstruction (loss of forced expiratory volume), but they could find no relationship between mucous

TABLE 4.—Prevalence of abnormalities in tests of small airway function in smokers

Author Year Country Reference	Number and type of population	Sub-groups	% smokers with abnormal test[a]							
			CV%	CC%	$\frac{\Delta N_2}{L}$	VisoV	V_{max25}	V_{max50}	$FEV_{1.0}$	FEV%
Buist, A.S. 1973 USA (*20,21*)	524 cigarette smokers attending an emphysema screening center	all smokers	35	44	47				11	
		<20 pack years	28	31						
		20–40 pack years	33	45						
		>40 pack years	49	64						
Benson, M.K. 1974 Great Britain (*12*)	214 heavy male smokers, aged 20–55; 75 non-smoking controls	young (20–30)	12		6				4	
		middle aged (40–55)	34		21				20	
Dirksen, H. 1974 Sweden (*41*)	58 randomly selected smokers, aged 59; 38 nonsmoking controls		53	66					43	
Hutcheon, M. 1974 Canada (*72*)	17 mild smokers selected from hospital personnel, aged 27.6 ± 3.2 years; 18 age-matched controls[b]			23.5		48[c]–67[d]				12
Marco, M. 1976 Belgium (*103*)	71 volunteer smokers with *normal* spirometric testing	Smokers	18.5		20.3					0
		Ex-smokers	11.7		11.9					0
		All smokers	23.9		25					0

TABLE 4.—Prevalence of abnormalities in tests of small airway function in smokers—Continued

Author Year Country Reference	Number and type of population	Sub-groups	% smokers with abnormal test[a]							
			CV%	CC%	$\frac{\Delta N_2}{L}$	VisoV	V_{max25}	V_{max50}	$FEV_{1.0}$	FEV%
McCarthy, D.J. 1976 Winnipeg (*106*)	131 volunteers from a smoking cessation clinic - varying smoking history[b]		48	9	42				30	13
Armstrong, J.G. 1976 Australia (*7*)	101 asymptomatic smokers and 20 nonsmoking controls aged 18–39	iight smokers heavy smokers	10 30		28 34				0 4	
Fairshter, R.D. 1977 USA (*50*)	18 asymptomatic mild smokers aged 29.8±5.4 yrs. 24 volunteer non-smoking controls	none				55.6				
Knudson, R.J. 1977 USA (*85*)	1900 white randomly selected subjects aged 25-54. (426 smokers)	symptomatic smokers (n=150) asymptomatic smokers (n=276)	9.1 6.0	12.9 8.7	30.4 15.4					
Cherniack, R.M. 1977 USA, Canada (*31*)	1456 randomly selected subjects from 3 cities (40% smokers) aged 25-54.	Montreal (n=275) Men Women	 15 14	 28 17	 14 19					 10 14
		Portland (n=208) men women	 15 36	 22 30	 17 47					 3 15

TABLE 4.—Prevalence of abnormalities in tests of small airway function in smokers—Continued

Author Year Country Reference	Number and type of population	Sub-groups	% smokers with abnormal test[a]							
			CV%	CC%	$\frac{\Delta N_2}{L}$	VisoV	V_{max25}	V_{max50}	$FEV_{1.0}$	FEV%
Cherniack, R.M. 1977 USA, Canada (*31*) (Cont'd)	1456 randomly selected subjects from 3 cities (40% smokers) aged 25-54.	Winnipeg (n = 112)								
		men	14	28	12					23
		women	20	26	20					26
		combined	17	25	23					
Oxhoj, H. 1977 Sweden (*114*)	502 randomly selected 50 and 60 year old male smokers - 129 nonsmoking controls[b]	50-year-old men								
		ex-smokers	13	18	32		2	5	10	10
		moderate smokers	9	15	41		3	5	18	7
		heavy smokers	12	20	58		7	10	37	22
"	"	60-year-old men								
		ex-smokers	10	17	18		2	4	15	10
		moderate smokers	19	24	38		2	17	22	18
		heavy smokers	23	22	45		1	18	22	22
Manfreda, J. 1977 Canada (*98,100*)	534 randomly selected smokers and ex-smokers aged 24–55	Men (n = 301)								
		Smokers	21.1	28.7	45.4		24.1	19.8	13.4	12.8
		ex-smokers	14.2	17.0	25.5		22.8	21.9	11.4	7.9
		Women (n = 233)								
		smokers	6.7	6.7	45.3		24.7	32.3	25.9	8.2
		ex-smokers	4.4	5.9	19.1		12.0	20	18.7	6.7

Footnotes on following page.

TABLE 4.—Footnotes

FEV = Forced expiratory volume
$FEV_{1.0}$ = FEV in 1 second
VC = vital capacity
FVC = forced vital capacity
FEV% = $FEV_{1.0}$/FVC x 100
V_{max} = maximum flow
V_{max} 50 = maximum flow at 50% of vital capacity
V_{max} 25 = maximum flow at 25% of vital capacity
CV = closing volume
RV = residual volume
TLC = total lung capacity
CV% = CV/VC x 100
CC% = (RV + CV)/TLC x 100
$\Delta N_2/L$ = slope of the alveolar plateau
VisoV = volume of isoflow

[a]abbreviations and definitions of pulmonary function tests
[b]estimated from bar graph
[c]obtained from spirometry
[d]obtained from plethysmography

hypersecretion and airflow obstruction. They suggested that there is a susceptible population of smokers who develop a more rapid decline in forced expiratory volume, eventuating in severe obstructive lung disease.

Pathological evidence of the effects of smoking on small airway histology was presented by Niewoehner, et al. (*112*) in an autopsy study of 39 men (20 nonsmokers, 19 smokers) who died suddenly from nonrespiratory causes. They observed a respiratory bronchiolitis in the lungs of smokers but rarely observed these changes in nonsmokers ($p<0.002$). They postulated that these changes were precursors of emphysema and responsible for the subtle function abnormalities observed in young smokers. In a second autopsy study of 168 male victims of sudden death aged 16 to 65, Kleinerman and Rice (*83*) age-matched 18 nonsmokers and 18 smokers. They observed significantly more chronic bronchiolitis, emphysema, and parenchymal pigmentation in lung tissue in smokers versus nonsmokers.

Prospective pathological evidence that abnormalities in tests of small airway function reflect structural alterations in small airways has recently been presented by Cosio, et al. (*37*). They examined the relationship between preoperative pulmonary function tests and graded pathologic lesions in the small airways (Group I-IV) in 36 patients (30 smokers, 4 ex-smokers, 2 nonsmokers) who went to surgery for an open lung biopsy (localized disease). These data are presented in Figure 1. Subjects with the lowest pathological score (Group I) were younger, had smoked fewer cigarettes, and had a normal FEV_1 percent. Subjects with minimal pathologic changes, Group II, could be separated from Group I (least pathological changes) by several tests of small airway function (closing capacity, volume of isoflow comparing air and helium on the flow volume curve, and slope of the alveolar plateau). The mean cigarette consumption in Group II was more than twice that of Group I. Group II-IV subjects demonstrated progressively abnormal function tests but only Group IV demonstrated a substantial amount of emphysema. The authors concluded that structural abnormalities in the small airways can be detected in living patients with normal FEV_1 percent by tests of small airway function. However, as noted by Thurlbeck (*140*), the maximum mid-expiratory flow rates also showed changes that were close to significant in Group I and II diseases.

These findings lend support to the postulated natural history of smoking induced lung changes advanced by Dosman, et al. (*44, 45*). They suggest that the effects of smoking on the lung are sequential, beginning with changes in the peripheral airways and progressing through stages of alterations in the mechanical properties of alveolar walls and loss of elastic recoil, and finally leading to the overt development of chronic bronchitis and emphysema with a reduction of

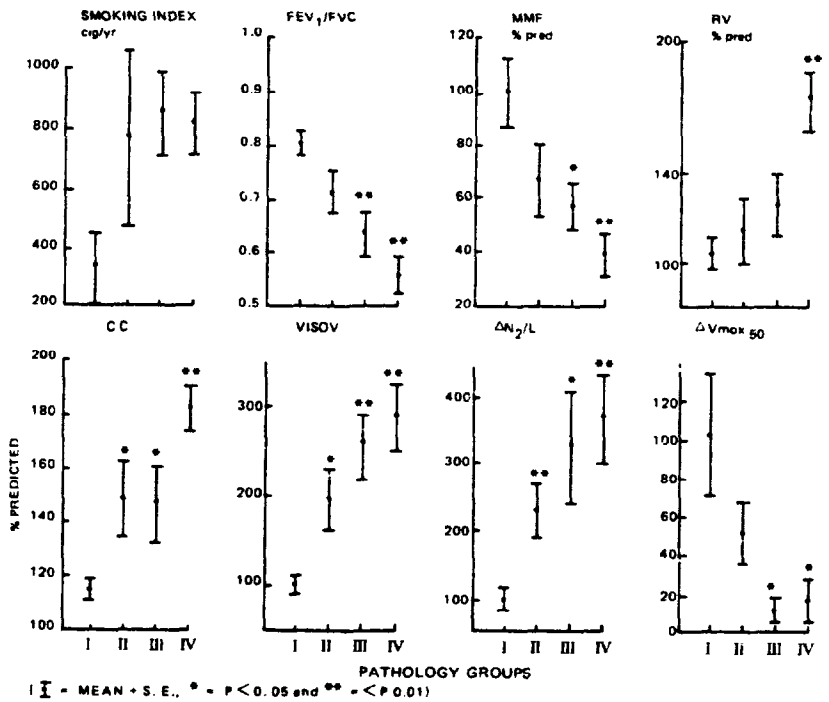

FIGURE 1.—Comparison of increasing small airways disease (Group I–IV) to smoking and pulmonary function

SOURCE: Cosio, M. (*37*)

FEV_1 percent. However, the mechanisms responsible and the demonstration of such a sequence remain to be demonstrated.

In summary, a variety of function abnormalities believed to represent small airway dysfunction occur in smokers. Many such individuals demonstrate normal expiratory flow rates as measured by conventional spirometry. In one prospective study abnormalities in tests of small airway function appeared to correlate well with pathologic abnormalities of the peripheral airways. It has been suggested that such changes may be precursors of further abnormality if smoking were continued; however, prospective studies relating small airway physiological and/or pathological abnormalities to the subsequent development of COLD are lacking.

Respiratory Morbidity in the Adult

In 1970, in the United States, the combined prevalence of chronic bronchitis for members of both sexes over age 17 was 29.5 per 1,000

population, and for emphysema it was 9.8 per 1,000 population. In 1970, persons with chronic bronchitis lost, on the average, 1.4 workdays per year, while those with emphysema lost more than 5 workdays per year due to disability from these diseases.

The relationship between smoking and an increased prevalence of respiratory symptoms in the adult has been well established in studies of hospital and clinic patients, working groups, total communities, and representative samples of the community (*141, 145*). Such symptoms, particularly cough and sputum production, increase with increasing dosage of cigarettes smoked. The association of smoking with wheezing is similar, though less marked, to that seen with cough and sputum. Chest illness during the past 3 years, cough lasting 2 weeks or more, and breathlessness are usually more prevalent in smokers than in nonsmokers, but evidence for a dose-response is inconsistent. This may be related to a decision by the smoker to reduce cigarette consumption upon recognition of such symptoms (*67*).

COLD is more common in men than in women; however, these differences must be corrected for differences in the smoking habit, since there are more male than female smokers. A number of earlier studies found conflicting data regarding the prevalence of symptoms in women with smoking habits equivalent to those in men (*139*).

Lebowitz and Burrows (*90*), in a recent study of 2,857 randomly selected subjects aged 14 to 96, found no significant differences in the prevalence of symptoms in younger men and women with equivalent smoking habits. However, male symptom rates were consistently higher above the age of 60 and in ex-smokers with a greater than 20 pack-year smoking history.

In a survey of 500 working women, aged 25 to 54, Woolf (*161*) noted a strong correlation between the number of cigarettes smoked and the prevalence of respiratory symptoms (cough, sputum production, wheezing, and shortness of breath). In comparing these results to published data on men, Woolf concluded that smoking had similar adverse effects on the respiratory system in women and men.

The relationship between smoking and acute respiratory infection was examined by Monto, et al. (*110*) in individuals with COLD and in two similar groups (comparable in age, sex, number of family members) with no history of flow obstruction or chronic bronchitis. The presence of respiratory illness was ascertained weekly, usually by telephone. The presence of infection was evaluated by serological tests for several viruses, Mycoplasma pneumoniae, and Hemophilus influenzae performed three times during the year. Among bronchitics, infections (as measured by serological tests) were more frequent in smokers than in nonsmokers; however clinical respiratory illness was greater in nonsmokers. The authors suggest that this disparity may be due to different perception of mild symptoms as disease in the two groups.

In summary, these data suggest that adult cigarette smokers have respiratory symptoms more frequently than do nonsmokers and that at least some symptoms (i.e., cough and sputum production) increase with a greater dosage of cigarettes. While it is clear that COLD is more common in men than in women, it is uncertain whether men and women with equivalent smoking histories have a similar increase in the prevalence of respiratory symptoms and COLD.

Ventilatory Function

Subtle, functional abnormalities (i.e., in tests of small airway function) have been recognized in smokers in whom standard spirometric measures are normal. These studies were reviewed in a previous section. It is generally recognized that the standard pulmonary function tests only become abnormal late in the pathological process, perhaps after some irreversible structural changes have occurred.

The majority of epidemiological surveys investigating the prevalence of functional abnormalities in smokers have employed measurements of ventilatory capacity, usually FEV. Measurements of airways resistance, diffusing capacity, lung volumes, and nitrogen mixing have been used much less frequently.

These studies, which were recently reviewed by Higgins (*67*), have confirmed that lung function is consistently worse in smokers than in nonsmokers. One major exception to this finding was a report on a study from the Kaiser Permanente multiphasic health check clinic (*128*) in which 65,086 white, black, and oriental smokers and nonsmokers, aged 20 to 79, answered a self-administered questionnaire about smoking habits and underwent pulmonary function testing. Significant differences were observed between white male and female smokers and nonsmokers with respect to their performance on pulmonary function tests. However, differences were not observed between black and oriental smokers and nonsmokers. An explanation was not readily apparent.

In a survey of New York City postal and transit workers, Densen, et al. (*40*) found the lowest values for FEV_1 among cigarette smokers. Stebbings (*133*), in a further analysis of Densen's data, noted significantly less decline in FEV_1 among black smokers when compared to white smokers. This difference persisted even when corrections were made for differences in amount smoked, age at which smoking began, inhalation patterns, and smaller initial lung volumes in blacks. Black and white nonsmokers did not differ in the rate of decline in FEV_1. By age 60, blacks who smoked one pack per day had a .34 liter smaller cumulative decrease in FEV_1 than whites who smoked the same amount.

In a study of male-female differences in pulmonary function of young smokers with similar smoking history, Enjeti, et al. (*47*) found abnormalities in tests of small airway function in males, but not in

female smokers. They suggested that men respond differently to habitual cigarette smoking at an earlier stage than do women.

Few reports have shown a consistent dose-response relationship between cigarette smoking and functional abnormality. In a recent study, Burrows, et al. (*23*) demonstrated an inverse relationship between ventilatory function and pack-years, even in subjects who denied cough and sputum.

The long-term effects of cigarette smoking on lung function have been examined in several prospective studies. These have usually shown that the rate of decline of FEV in smokers is greater than in the nonsmoker (*67*). This was again suggested in the 10-year followup of the Framingham cohort (*8*).

In a large prospective study of London working men, Fletcher, et al. (*57*) recognized a "susceptible" group of smokers whose rate of decline in FEV was steeper than that for nonsmokers. However, there was another group of smokers who lost FEV almost as slowly as did nonsmokers. The authors suggest that the effect of smoking on FEV in "susceptible" individuals may be underestimated by focusing on the mean FEV of all smokers, as is usually done in prevalence surveys. As noted earlier, they found no relationship between the rate of decline in FEV and productive cough when smoking habits were taken into account. This is in conflict with Gregg's data (*62*), in which only smokers with bronchial hypersecretion were likely o develop functional decline.

In summary, the majority of epidemiological surveys have found a higher prevalence of functional abnormalities in smokers as compared to nonsmokers. There are conflicting data as to the effect of smoking on pulmonary function in different racial groups and whether men and women with equivalent smoking habits have similar reductions in pulmonary function. It is clear that cigarette smoking produces a more rapid decline in FEV and a higher prevalence of productive cough. However, it is unclear whether the presence of productive cough by itself predicts the risk for a more rapid decline in FEV independent of that increased risk associated with cigarette smoking. It has been suggested that there may be a "susceptible" group of smokers whose rate of decline in FEV is much greater than that in both "unsusceptible" smokers and nonsmokers and that "unsusceptible" smokers and nonsmokers have similar rates of decline in FEV. Therefore, prevalence surveys of functional abnormalities in all smokers may underestimate the impact of cigarette smoking in the "susceptible" population.

Cessation and Reversibility of Functional Changes

Smoking cessation results in a reduced prevalence of symptoms in all age groups and in reduced mortality rates. The effects of smoking cessation on pulmonary function have been considered at various stages of functional abnormality.