CONTENTS

INTRODUCTION

Obstructive airways diseases constitute a heterogeneous group of disorders that include but are not limited to emphysema, asthma, chronic bronchitis, and chronic obstructive pulmonary disease (COPD). These four clinical conditions are the most prevalent of the obstructive airways diseases and are responsible for substantial morbidity and mortality. Over 18 million Americans suffer from asthma, and about 12 million Americans have COPD, which is the fifth leading cause of death and the most rapidly increasing cause of death among adults older than 65 years (Feinleib et al. 1989). The 1984 Report on the health consequences of smoking reviewed information on chronic obstructive lung diseases (US DHHS 1984). The Report concluded that "cigarette smoking is the major cause of chronic obstructive lung disease in the United States for both men and women. The contribution of cigarette smoking to chronic obstructive lung disease morbidity and mortality far outweighs all other factors" (US DHHS 1984, p. 8). Approximately 84 percent of COPD mortality among men and 79 percent among women is attributable to cigarette smoking (US DHHS 1989). The annual toll of smoking-attributable COPD in the United States is estimated to be 57,000 deaths (US DHHS 1989), which are responsible for more than 500,000 years of potential life lost before the average life expectancy (Davis and Novotny 1989).

The nosology of obstructive airways diseases has been evolving since the CIBA Foundation Guest Symposium in 1959, one of the first attempts to create a standardized classification. For the purposes of this Chapter, emphysema refers to pathologic abnormal permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of airspace walls and without obvious fibrosis (American Thoracic Society 1987). Chronic bronchitis refers to chronic cough and/or sputum production for at least 3 months per year for 2 consecutive years. Asthma has been defined as "a disease characterized by increased responsiveness of the airways to various stimuli and manifested by slowing down of forced expiration, which changes in severity either spontaneously or as a result of therapy" (American College of Chest Physicians, American Thoracic Society Joint Statement 1975). The term COPD is used to describe persistent obstructive ventilatory impairment as determined by a test of pulmonary ventilatory function (O'Connor, Sparrow, Weiss 1989).

Overlap of these conditions is extremely common, although discrete cases of each can be identified (Figure 1). It is estimated that 60 to 100 percent of COPD patients also have airways hyperresponsiveness (Klein and Salvaggio 1966; Parker, Bilbo, Reed 1965; Ramsdell, Nachtwey, Moser 1982; Ramsdale et al. 1984; Bahous et al. 1984). Almost one-half of all asthmatics suffer from chronic bronchitis (Burrows et al. 1987), and asthma may be a risk factor for the development of chronic airflow obstruction (Fletcher et al. 1976; Schachter, Doyle, Beck 1984; Buist and Vollmer 1987; Peat, Woolcock, Cullen 1987). Although the extent of emphysema, as documented by postmortem examination of the lungs, correlates significantly with the degree of fixed airflow obstruction, the correlation is modest, suggesting that emphysema alone does not fully explain the functional impairment in most persons with COPD (Cosio et al. 1977).
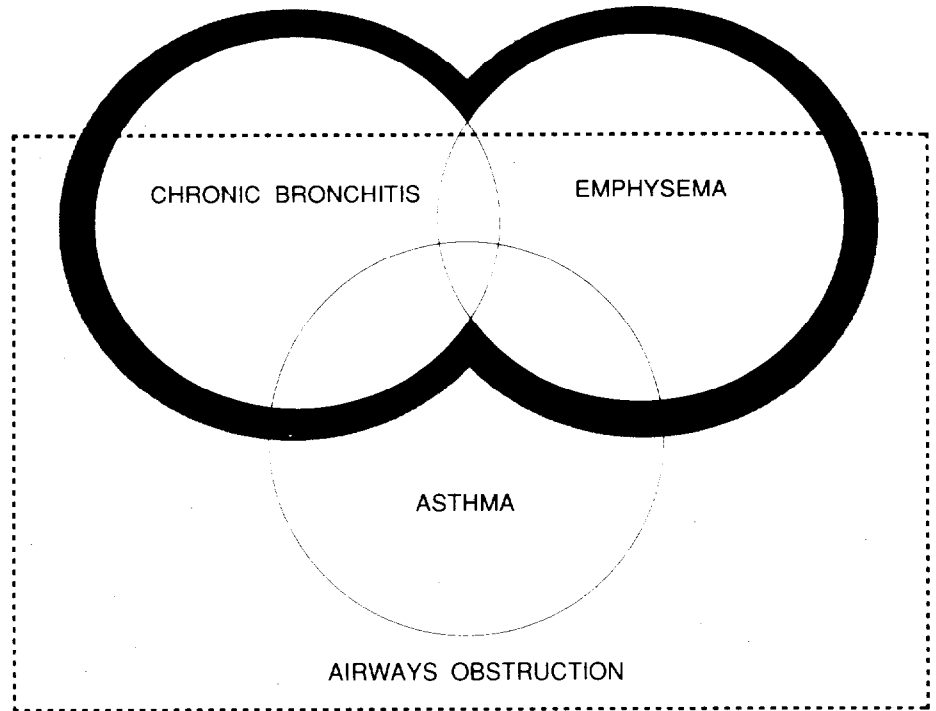
FIGURE 1.—Nonproportional Venn Diagram of the interrelationship among chronic bronchitis, emphysema, asthma, and airways obstruction.

SOURCE: Snider (1988).

Researchers in the United States and the United Kingdom tend to separate asthma from the other obstructive airways diseases and to deemphasize the importance of cigarette smoking in this particular clinical entity. However, the data suggest that cigarette smoking may influence asthma and that allergy and airway hyperresponsiveness, strongly associated with asthma, may play a role in the development of fixed airflow obstruction (O'Connor, Sparrow, Weiss 1989).

The generally accepted model of the pathogenesis of COPD is based on the results of longitudinal investigations of lung function (Fletcher and Peto 1977; Becklake and Permutt 1979; Burrows 1981; Speizer and Tager 1979) (Figure 2). The model suggests that disease development is preceded by a long latent period during which lung function declines at an accelerated rate.

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FEV₁ as %
of value at
age 20-25

(Graph showing curves labeled A, B, C, D, E, F, G with FEV₁ axis values 100, 75, 50, 25, horizontal dashed lines labeled "Disability" and "Death", and AGE-years axis from 5 to 80)
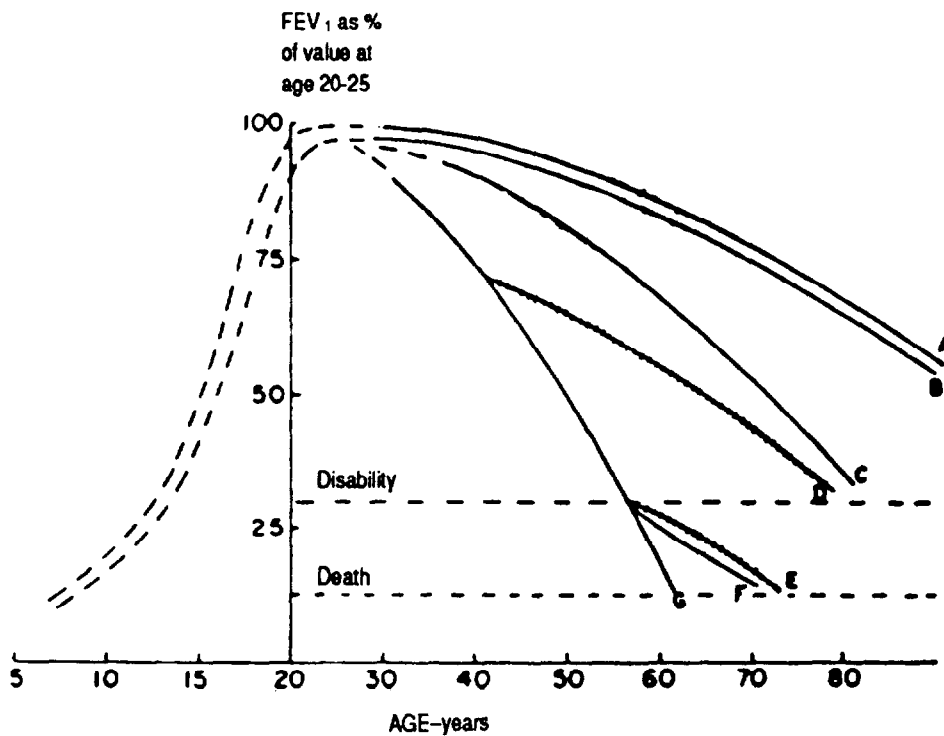
FIGURE 2.—Theoretical curves depicting varying rates of decline of FEV₁

NOTE: Curves A and B represent never smokers and smokers, respectively, declining at normal rates. Curve C shows increased decline without development of COPD. Rates of decline for former smokers are represented by curves D and E for those without and with clinical COPD, respectively. Curves F and G show rates of decline with continued smoking after development of COPD.

SOURCE: Speizer and Tager (1979).

Several features of this conceptual model merit emphasis in relation to smoking. First, disease development may occur as a result of factors that accelerate decline in adult life, lead to less than maximal growth, or both. Second, because of the extremely long latent period from the onset of smoking to disease development, factors important in childhood and young adulthood cannot be addressed in longitudinal studies that begin in adulthood. Third, longitudinal studies of children and adults have shown that pulmonary function levels are very stable over time with tracking correlations ranging from 0.70 to 0.90. This high degree of longitudinal correlation, consistent with both environmental and genetic determinants of disease, demonstrates the importance of previous level of function as a major determinant of future disease risk.

Research on risk factors for COPD was reviewed extensively in the 1984 Report of the Surgeon General (US DHHS 1984). The review leads to several general findings

with regard to smoking. Cigarette smoking is associated with low levels of 1-sec forced expiratory volume (FEV_1) in cross-sectional investigations (Knudson, Burrows, Lebowitz 1976; Burrows et al. 1977; Beck, Doyle, Schachter 1981; Dockery et al. 1988; US DHHS 1984), with accelerated decline of FEV_1 in longitudinal studies (Burrows et al. 1987; Beck, Doyle, Schachter 1982; Bossé et al. 1981; US DHHS 1984), and with increased mortality from COPD (Best 1966; Doll and Peto 1976; Hammond 1965; Hammond and Horn 1958; US DHHS 1984). The effects of cigarette smoking on lung function level or rate of decline and on mortality increase with the duration and amount of smoking (US DHHS 1984).

Because the development of COPD in adults is associated with a long latent period, the age at which cigarette smoking might have a critical effect has not readily been addressed. Passive smoking impairs lung growth in children and thus, may limit maximal lung growth (Tager et al. 1983; US DHHS 1986). Smoking in adults may shorten the phase when lung function tends to plateau between the ages of 20 and 40 and/or may accelerate the decline in lung function (Tager et al. 1988). Cigarette smoking is the predominant cause of lung function decline at a rate greater than the annual volume loss of 20 to 30 mL associated with aging.

Although cigarette smoking has been clearly established as the major risk factor for COPD, the interactions of the intensity of smoking with factors determining susceptibility have not been fully characterized. For example, Burrows and coworkers (1987) suggested that two subsets of COPD patients can be differentiated by the presence or absence of accompanying asthmatic features. According to this hypothesis, subjects with chronic asthmatic bronchitis have a better long-term prognosis, smaller cumulative exposure to tobacco smoke, and greater prevalence of allergy and airway responsiveness. The second group of patients has emphysema, poorer long-term prognosis, greater cumulative tobacco smoke exposure, and reduced prevalence of allergy and airway hyperresponsiveness (Burrows et al. 1987). Available data do not discriminate the relative contributions of cigarette smoking in these clinical subtypes of patients.

Studies of the mechanisms by which cigarette smoking causes lung injury were reviewed extensively in the 1984 Report of the Surgeon General (US DHHS 1984). That Report and other reviews (Thurlbeck 1976; Snider 1989; Wright 1989) also cover the relationship between the structural changes associated with smoking and the severity of airflow obstruction. Cigarette smoking causes inflammation of both the airways and parenchyma of the lung; the resulting structural damage has functional consequences that can lead to the development of clinically diagnosed COPD if there is sustained smoking. Frank parenchymal damage is preceded by an increase in inflammatory cells in lung parenchyma at the level of the bronchioli (Niewoehner, Kleinerman, Rice 1974). Both neutrophils and alveolar macrophages are important in the development of this inflammatory bronchiolitis. Although neutrophils store and release greater quantities of elastase than alveolar macrophages (Janoff et al. 1979), the macrophage may be an important cell in attracting neutrophils to the lung (Hunninghake and Crystal 1983). Cigarette smoking-induced bronchiolitis is associated with functional abnormalities detectable in the early stages only with sensitive tests of small airway function (Buist et al. 1979; Cosio et al. 1977; McCarthy, Craig, Cherniack 1976; Ingram and Schilder 1967; Ingram and O'Cain 1971). Even before significant em-

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physema is present, destruction of peribronchiolar alveoli can be found in the lungs of smokers (Saetta et al. 1985; Wright 1989); the loss of alveolar attachments may result in loss of elastic recoil (Wright 1989).

The protease–antiprotease hypothesis proposes that the destruction of lung tissue resulting in emphysema occurs as a consequence of genetic or acquired imbalance of proteolytic and antiproteolytic enzymes in the lung. As noted in the 1984 Surgeon General's Report (US DHHS 1984), this theory derives from two principal observations: (1) α-1-antitrypsin, a major anti-elastolytic enzyme of the lower respiratory tract, is absent in persons genetically deficient in α-1-antitrypsin; these persons often develop emphysema at an early age (Laurell and Eriksson 1963), and (2) administration of proteolytic enzymes in animal models produces emphysema (Gross et al. 1965). Cigarette smoking is associated with increased numbers of neutrophils and activated macrophages in the lungs of smokers, and neutrophil elastase can cause emphysema in animal models (Harris et al. 1975; Galdston et al. 1984). In addition, the α-1-antiprotease of cigarette smokers has reduced functional activity (Gadek, Fells, Crystal 1979; Gadek et al. 1981).

However, although damage to the airways and parenchyma of the lung by cigarette smoke underlies excess lung function loss and COPD in smokers, the factors determining the development of disease in individual smokers have been only partially characterized. A minority of cigarette smokers develop COPD, and cigarette smoking only partially explains the variability in FEV_1 decline (Burrows et al. 1977; US DHHS 1984). Data suggest that cigarette smoking may influence airway as well as parenchymal inflammation. Thus, host factors determining the response of the airways and parenchyma to cigarette smoking, as well as the intensity of smoking, are likely to determine the development of disease.

Cigarette smoking has a variety of effects on the immune system; those effects may be important in determining the risks of COPD and other respiratory diseases. Cigarette smoking is associated with elevated total serum IgE. This total IgE does not exhibit seasonal variability, as seen in atopic individuals, and the antigens responsible for this increase have not been identified. Cigarette smoking may influence the development of an atopic diathesis via effects on T-cell helper and suppressor activity (Ginns et al. 1982; Miller et al. 1982), epithelial permeability (Jones et al. 1980; Simani, Inoue, Hogg 1974), or functional alterations of antigen-presenting cells (Warr and Martin 1977). Cigarette smoking is associated with skin test positivity among children exposed to maternal cigarette smoking (Weiss et al. 1985; Martinez et al. 1988); however, this association is not seen in studies of active adult smokers (Burrows, Lebowitz, Barbee 1976). In adult subjects, skin test positivity is most prevalent among former smokers (Taylor, Gross et al. 1985). These data are consistent with the hypothesis that atopic individuals may not become or remain regular smokers because of airway inflammation secondary to inflammatory effects of cigarette smoking. Thus, cigarette smoking may interact with atopy in a complex manner, inducing atopy in less susceptible or initially nonatopic subjects and discouraging highly atopic subjects from taking up smoking.

Eosinophils are primary effector cells for allergic inflammation (DeMonchy et al. 1985). Increases in eosinophils are associated with the severity and exacerbations of asthma (Horn et al. 1975). Increased eosinophils are also associated with the occurrence

of respiratory symptoms and the level of pulmonary function (Burrows et al. 1980; Kauffman et al. 1986). Cigarette smokers exhibit elevations of the peripheral blood eosinophil count (Taylor, Gross et al. 1985), although it is unknown if allergen-induced and cigarette smoking-induced eosinophilia occur by similar or different mechanisms. Eosinophils in peripheral blood are also related to clinical correlates of emphysema (Nagai, West, Thurlbeck 1985).

Cigarette smoking has also been associated with increased levels of airway responsiveness (Woolcock et al. 1987; Sparrow et al. 1987; Burney et al. 1987). Several mechanisms could explain the relationship between cigarette smoking and increased airway responsiveness, including smoking-associated reduction in prechallenge level of lung function, chronic airway inflammation due to smoking, and smoking-induced impairment of epithelial function. The potential central role of cigarette smoking in parenchymal and airways inflammation is depicted in Figure 3.
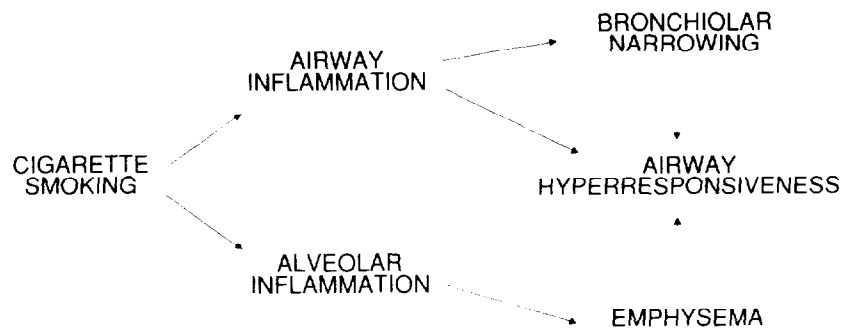
FIGURE 3.—Hypothesized mechanisms by which airway hyperresponsiveness may be associated with developing or established COPD without necessarily being a preexisting risk factor

NOTE: COPD=chronic obstructive pulmonary disease.

SOURCE: O'Connor, Sparrow, Weiss (1989).

When considered in this pathophysiologic framework, the potential consequences of smoking cessation on the degree of impairment and future risk of COPD vary with the extent of irreversible changes at cessation and with host characteristics of the quitting smoker. In adults, cigarette smoking cessation is associated with a slowing of FEV_1 decline to the rate of never smokers (Figure 2). To the extent that airway and alveolar inflammation have caused reversible epithelial and parenchymal inflammation, pulmonary function could improve after cessation, particularly if heightened airway responsiveness and bronchiolitis can resolve. To the extent that cigarette smoking has caused permanent damage to lung structure (e.g., emphysema), those changes are

unlikely to be reversible. Thus, the amount and duration of smoking, the relative extents of parenchymal and airway inflammation, and the degree of permanent structural damage are probably the key determinants of the level of function after smoking cessation. Even in the setting of established COPD, smoking cessation may potentially reduce the rate of functional loss.

Former smokers may differ from continuing smokers with regard to host characteristics that potentially determine susceptibility to cigarette smoke. Because presmoking levels of atopy and airway responsiveness modify the short-term response to smoke, individuals with atopy or heightened airway responsiveness may be less likely to take up smoking, to reduce smoking, or to quit smoking if respiratory symptoms occur. This potential bias, termed the "healthy smoker effect" by O'Connor, Sparrow, and Weiss (1989), cannot be evaluated in cross-sectional studies.

PART I. SMOKING CESSATION AND RESPIRATORY MORBIDITY

Respiratory Symptoms

Since the 1950s, strong evidence has accumulated documenting increased respiratory symptoms in smokers of all ages compared with nonsmokers (US PHS 1964; US DHEW 1971, 1979; US DHHS 1984). Further, the number of cigarettes smoked per day is the strongest risk factor for the principal chronic respiratory symptoms including chronic cough, phlegm production, wheeze, and dyspnea (Lebowitz and Burrows 1977; Dean et al. 1978; Higgins, Keller, Metzner 1977; Huhti and Ikkala 1980; Higenbottam et al. 1980; Schenker, Samet, Speizer 1982). The widespread effects of chronic smoking on the lung, including decreased tracheal mucous velocity (Lourenço, Klimek, Borowski 1971; Goodman et al. 1978; Thomson and Pavia 1973), increased secretion of mucus on the basis of mucous gland hypertrophy and hyperplasia (Thurlbeck 1976), chronic airway inflammation (Niewoehner, Kleinerman, Rice 1974), increased epithelial permeability (Jones et al. 1980; Minty, Jordon, Jones 1981; Mason et al. 1983), and emphysema (US DHHS 1984), underlie the development of these symptoms. Smoking cessation has been associated with a reduction in respiratory morbidity, presumably through reversal of some of these pathophysiologic abnormalities. Relevant evidence can be found in clinical studies, which involve followup of the symptoms of persons participating in smoking cessation clinics, and epidemiologic studies.

Clinical Studies

Buist and coworkers (1976) found that smoking cessation was associated with a dramatic reduction in respiratory symptoms within 1 month of cessation. These researchers assessed spirometry and respiratory symptoms for over 12 months in 75 cigarette smokers enrolled in a smoking cessation program. Subjects were divided into quitters (those who did not smoke during the entire 12-month period), modifiers (individuals who reduced their cigarette consumption by 25 percent), and nonmodifiers

(subjects who continued to smoke at the same level). The three groups were of comparable ages (35 to 39 years) and had a cumulative cigarette consumption of 20 to 26 pack-years. A symptoms ratio was calculated at 1, 3, 6, and 12 months by taking the number of symptoms (e.g., cough, expectoration, shortness of breath, and wheezing) observed and dividing by the total number of possible symptoms for that group. All groups started with ratio values of approximately 0.55. The ratios for quitters declined within 1 month of cessation and continued to decline over the course of the study from 0.52 to 0.08. In contrast, the ratios for modifiers decreased less than quitters, and nonmodifiers had no change in their ratios over 12 months (Figure 4). Data on individual symptoms were not presented, and smoking abstinence was not verified by biologic markers. In a followup study of more than 30 months, Buist, Nagy, and Sexton and colleagues (1979) again showed that among 15 quitters, respiratory symptoms disappeared by the third or fourth month of followup and did not return during the remainder of the study. However, after a small initial decrease in symptoms among 45 continuing smokers, further decreases were not recorded. The small sample sizes and a 41-percent loss to followup must be considered in interpreting the latter findings.

Three studies reported different results for the effect of smoking cessation on respiratory symptoms in asthmatics. Higenbottam, Feyeraband, and Clark (1980) conducted a cross-sectional study of 106 consecutive asthmatic clinic patients and concluded that symptoms decreased after stopping smoking. Age-standardized prevalence rates for chronic cough, chronic cough and phlegm, and wheezing among asthmatics were lower for the 27 former smokers than for the 27 current smokers and the 52 never smokers. Only breathlessness was found more often in former smokers than in the other smoking groups, possibly reflecting irreversible smoking-induced changes. Quantification of smoking history and time since cessation among former smokers was not reported. In contrast, Fennerty and colleagues (1987) as well as Hillerdahl and Rylander (1984) reported increased respiratory symptoms in asthmatics who stopped smoking. Fennerty and coworkers (1987) found that 2 of 14 asthmatics (14.3 percent) who stopped smoking for 24 hours complained that asthmatic symptoms were worsening. Neither of these two subjects showed a decrease in specific airway conductance or peak flow, but one had an increase in airway responsiveness to methacholine. However, four of seven asthmatics who abstained from smoking for 7 days recorded a reduction in symptoms. Hillerdahl and Rylander (1984) studied 59 asthmatics who were recruited from an office practice and who had stopped smoking "permanently or for short periods of time." Using questionnaires, these reseachers found that symptoms worsened in 18 asthmatics (30.5 percent) who had stopped smoking. Three subjects claimed onset of new asthmatic symptoms within months of cessation. Asthmatics younger than 40 years of age were more likely to complain of worsening of their asthma than those subjects older than 40 years of age. Hillerdahl and Rylander (1984) concluded that among asthmatics who smoke, psychological reasons, improved secretion clearance, or both could explain the findings. The uncontrolled nature of these studies, the small numbers of subjects, the potential for selection and information bias, and the noncomparability of treatment regimens among study participants limit the usefulness of these findings.
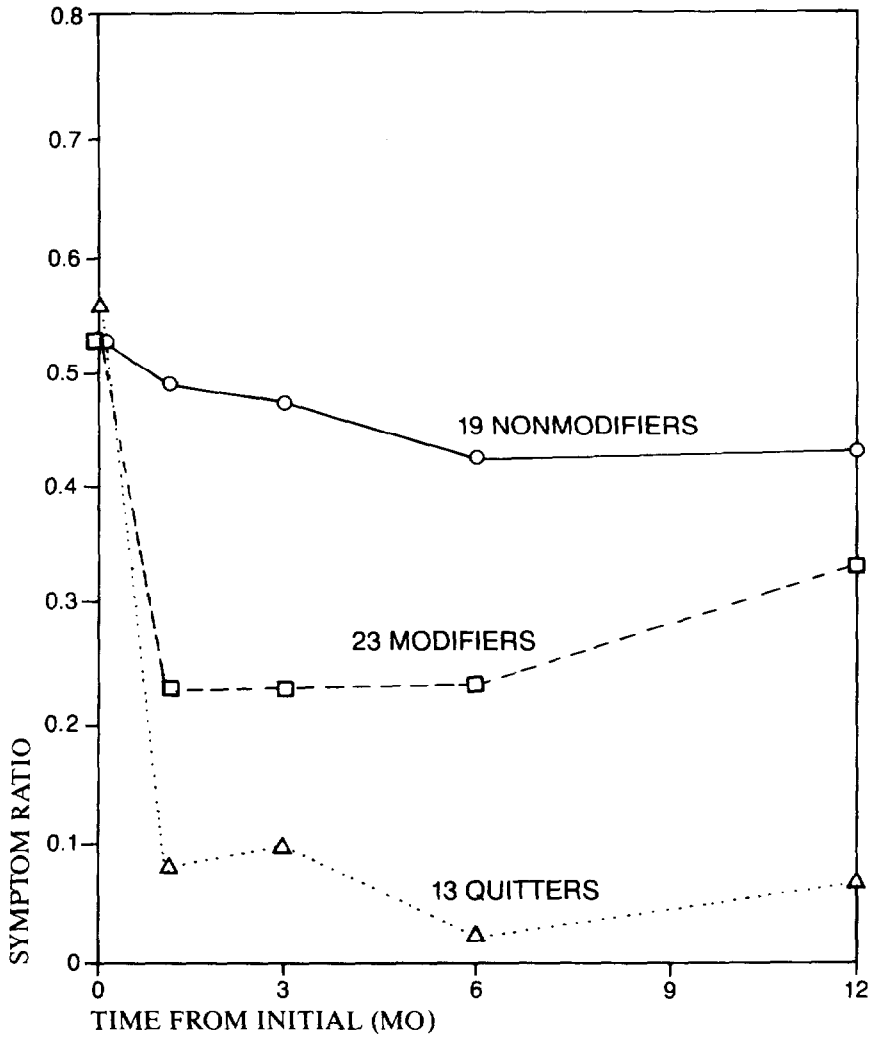
FIGURE 4.—Symptom ratio (number of observed symptoms to number of possible symptoms) in nonmodifiers, modifiers, and quitters at each test period; symptoms are cough, sputum production, wheezing, and shortness of breath

SOURCE: Buist et al. (1976).

In summary, studies of participants of smoking cessation clinics have shown that respiratory symptoms have disappeared rapidly on quitting, even after 20 pack-years of exposure. Limited studies of asthmatics have provided conflicting results.

Cross-Sectional Studies of Populations

The results of community-based studies have shown lower prevalence of respiratory symptoms among former smokers compared with current smokers (Table 1). Two early investigations evaluated symptoms of chronic nonspecific lung disease among smoking groups. Ferris and Anderson (1962) studied a random sample of subjects, aged 25 to 74, from an industrial town in New Hampshire. Using spirometry and interviewer-administered questionnaires, these researchers recorded lung function and symptoms associated with chronic nonspecific respiratory disease in 1,167 individuals. Chronic nonspecific respiratory disease was considered present if (1) phlegm production was reported six or more times per day for 4 days per week for 3 months per year for the past 3 years (chronic bronchitis); (2) if a diagnosis of asthma had been made and was still present; (3) if wheezing or whistling in the chest occurred most days or nights; (4) if shortness of breath occurred while walking at subject's normal pace on level ground; or (5) if an FEV_1 less than 60 percent of forced vital capacity (FVC) was noted (chronic obstructive lung disease). Age-standardized prevalence rates per 100 for chronic nonspecific respiratory disease showed that both male and female ex-smokers had rates of abnormality similar to those of never smokers and lower than those of current smokers (for males, 18.1 vs. 8.4 vs. 50.3, and for females, 17.2 vs. 19.2 vs. 31.0 for never smokers, ex-smokers, and current smokers, respectively). In 1967, a resurvey of the population using a slightly different random sample was performed (Ferris et al. 1971). Again, the age-standardized rates were less for both male and female ex-smokers than for current smokers.

Mueller and colleagues (1971) studied a random sample of one-fifth of the population of Glenwood Springs, CO. Symptoms of chronic nonspecific lung disease, comparable with those defined by Ferris and colleagues (1971), were reported by 20 percent of 55 male former smokers and by 9 percent of 22 female ex-smokers. These percentages were between those of current and never smokers. Age trends were not apparent among males; the small sample size precluded analysis for females.

In the mid-1960s, two surveys assessed the effects of smoking on respiratory symptoms in older men (Table 1). Wilhelmsen and Tibblin (1966) analyzed data from 339 men aged 50 years, born in 1913 and living in Göteborg, an industrial town in Sweden. Of 73 former smokers, the percentages with morning cough for 3 months per year, sputum for 3 months per year, and wheezing other than from colds were lower than those for 182 current smokers of less than or greater than 15 g of tobacco per day and similar to those of 84 never smokers. Dyspnea when walking fast or up a small hill was reported most frequently by current smokers of more than 15 g of tobacco per day; all other groups showed comparable percentages of subjects reporting this symptom.

Weiss and coworkers (1963) studied 350 consecutive men, aged 50 years or older, undergoing routine examination in the Philadelphia Pulmonary Neoplasm Research Project (N=6,137). Fifty-three percent of former cigarette smokers (N=68) reported one or more symptoms of cough, wheeze, or dyspnea compared with 57 percent of current smokers (N=183) and 42 percent of never smokers (N=36). Furthermore, former smokers complained of cough as frequently as never smokers (9 vs. 11 percent) and complained of dyspnea as often as current smokers (46 vs. 44 percent). Only 20

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TABLE 1.—Percentages of subjects in cross-sectional studies with respiratory symptoms, by cigarette smoking status and gender

Symptoms[a] Reference	Age (number of subjects)	Current smokers Male (%)	Female (%)	Former smokers Male (%)	Female (%)	Never smokers Male (%)	Female (%)
Cough 3 mo/yr							
Wilhelmsen and Tibblin (1966)	50 (339)	36.2	—	8.2		4.8	—
Weiss et al. (1963)	50–69 (287)	41.0	—	9.0	—	11.0	—
Fletcher and Tinker (1961)	40–59 (363)	19.9	—	13.0	—	0.0	—
Mueller et al. (1971)[b]	20–69 (892)	13.0	20.0	5.0	10.0	9.0	5.0
Manfreda, Nelson, Cherniack (1978)							
	25–54 (256)[c]	25.4	20.3	8.1	—	8.3	—
	25–54 (246)[d]	31.5	31.7	2.9	10.0	4.0	4.0
Schenker, Samet, Speizer (1982)[b]	17–74 (5,670)	—	9.1[e] 17.0[f] 31.8[g]	—	7.5	—	5.6
Phlegm 3 mo/yr							
Wilhelmsen and Tibblin (1966)		11.5	—	1.4	—	1.2	—
Fletcher and Tinker (1961)		17.6	—	16.9	—	7.5	—
Mueller et al. (1971)[b]		18.0	10.0	12.0	5.0	4.0	1.0
Manfreda, Nelson, Cherniack (1978)							
	25–54 (256)[c]	16.9	10.2	10.8	—	0.0	0.0
	25–54 (246)[d]	24.7	25.4	5.7	5.0	4.0	4.0
Hawthorne and Fry (1978)	45–64	36.2	23.0	16.1	10.9	10.1	6.7
Miller et al. (1988)[b]	Male (mean): 42.0 (1,169) Female (mean): 42.9 (1,169)	40.8	28.4	14.7	6.9	12.1	0.4

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TABLE 1.—Continued

Symptoms[a] Reference	Age (number of subjects)	Current smokers		Former smokers		Never smokers	
		Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
Schenker, Samet, Speizer (1982)[b]		—	7.2[e] 16.7[f] 24.8[g]	—	6.7	—	4.5
Lebowitz and Burrows (1977)	14–96 (2,857)	11.2	11.0	25.9	12.6	45.5	35.8
<u>Dyspnea grade[i]</u>							
Wilhelmsen and Tibblin (1966)[j]		24.7	—	21.9	—	20.2	—
Weiss et al. (1963)[j]		44.0	—	46.0	—	36.0	—
Fletcher et al. (1959) Grades 2 or more	40–59	23.5	29.0	25.0	23.1	10.0	31.4
Fletcher and Tinker (1961) Grade 3 or more		8.7	—	6.5	—	2.5	—
Mueller et al. (1971)[h] Grade 2,		29.0	32.0	14.0	41.0	22.0	32.0
Grade 3, or more		7.0	13.0	4.0	11.0	6.0	7.0
Manfreda, Nelson, Cherniack (1978)[k] Grade 2 or more	25–54 (256)[c]	5.6	22.1	5.4	6.1	8.3	7.0
	25–54 (246)[d]	12.3	17.5	5.8	5.0	4.0	12.0
Hawthorne and Fry (1978)[j]		13.2	18.6	9.9	20.5	7.0	13.2
Miller et al. (1988)[h] Grade 2		9.3	15.6	7.1	12.7	3.0	9.5
Grade 3		3.0	8.9	3.3	11.5	0.4	2.6
Schenker, Samet, Speizer (1982)[b] Grade 3		—	5.6[e] 6.1[f] 17.6[g]	—	8.2	—	5.9

TABLE 1.—Continued

Symptoms[a] Reference	Age (number of subjects)	Current smokers		Former smokers		Never smokers	
		Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
Wheeze							
Wilhelmsen and Tibblin (1966)[l]		12.6	—	6.9	—	4.8	—
Weiss et al. (1963)[m]		8.0	—	6.0	—	3.0	—
Fletcher et al (1959)[l]		16.3	12.9	12.5	—	—	2.3
Mueller et al. (1971)[h,l]		18.0	10.0	12.0	5.0	4.0	1.0
Manfreda. Nelson. Cherniack (1978)[n]							
	25–54 (256)[c]	26.8	25.4	10.8	12.1	4.2	3.5
	25–54 (246)[d]	31.5	30.2	14.3	20.0	8.0	8.0
Hawthorne and Fry (1978)[l]		21.8	19.2	9.8	10.6	6.1	6.0
Miller et al. (1988)[h,l]		40.8	28.4	14.7	6.9	12.2	7.4
Schenker. Samet. Speizer (1982)[h,l]		—	14.4[e] 18.5[f] 28.0[g]	—	8.3	—	6.0

[a]Symptoms not mutually exclusive.
[b]Age adjusted.
[c]Urban residents.
[d]Rural residents.
[e]1–14 cig/day.
[f]15–24 cig/day.
[g]≥25 cig/day.

[h]Weighted values to be representative of state as whole.
[i]Grade 2: dyspnea when walking with people of same age on level ground, grade 3: dyspnea when walking at one's own pace on level ground.
[j]Dyspnea not defined.
[k]Shortness of breath compared with persons of same sex and age.
[l]Ever wheeze.
[m]Wheezing not defined.
[n]Wheezing apart from colds.

men reported wheeze. precluding meaningful analysis for this variable. The high symptom rates seen in this study may reflect the older ages of the participants and the selection factors contributing to enrollment in the Philadelphia Pulmonary Neoplasm Research Project.

Three other early investigations confirmed a lower prevalence of specific respiratory symptoms among former smokers (Table 1). Fletcher and coworkers (1959) reported the respiratory symptoms of 244 British post office workers, aged 40 to 59, as part of the study of the relationship between symptoms and tests of lung function. Former smokers of both sexes reported wheezing on most days or nights less often than current smokers, but former smokers also complained of grade 2 dyspnea (i.e., stopping for breath when walking at one's own pace on level ground) as often as current smokers. Fletcher and Tinker (1961) studied respiratory symptoms in 363 London male transport workers. Former smokers had lower prevalence rates for cough. phlegm production. and grade 3 dyspnea (i.e., stopping for breath after walking about 100 yards on level ground) than current smokers of 15 cigarettes or more per day. In a large community-

based study in Tecumseh, MI. Payne and Kjelsberg (1964) reported age- and sex-specific prevalence rates for cough and phlegm production that were comparable for former and never smokers (Figure 5). In contrast, sex-specific rates of dyspnea were highest among former smokers and increased with age (Figure 6).

More recent studies have also found lower prevalence of respiratory symptoms among former smokers and documented sex-specific differences among smoking categories (Table 1). Mueller and colleagues (1971) showed that male former smokers had fewer symptoms than current smokers, including cough for 3 months per year, grade 2 dyspnea, and wheezing. Only sputum production for 3 months per year was higher among male former smokers than among never smokers. Female former smokers had lower prevalence rates for cough and phlegm production but higher rates for dyspnea and wheezing than current smokers. Rates for female former smokers were generally higher than those for male former smokers. Manfreda, Nelson, and Cherniack (1978) studied subjects from urban and rural communities in Canada, and found very similar overall and sex-specific prevalence rates for these respiratory symptoms among former smokers. In this study, however, female former smokers had prevalence rates between those of current and never smokers for all symptoms.

In three separate surveys, Hawthorne and Fry (1978) evaluated the association among smoking, respiratory symptoms, and cardiopulmonary mortality in 11,295 men and 7,491 women from southwest Scotland. Former smokers had prevalence rates for phlegm production and wheezing intermediate to those of current and never smokers. Male former smokers reported shortness of breath as often as male never smokers, whereas female former smokers had an increased prevalence of dyspnea compared with current smokers of either sex.

Miller and colleagues (1988) determined sex-specific prevalence rates for a wide range of respiratory symptoms in a stratified random sample from the general population of Michigan. Mean age for the three smoking groups was comparable. Male current and former smokers had similar lifetime cigarette pack consumption (9.09×10^3 vs. 9.93×10^3), whereas female current smokers had almost twice the cigarette consumption of former smokers (8.32×10^3 vs. 4.50×10^3). The prevalence rates of persistent sputum and wheezing were lower among male former smokers compared with current smokers. In contrast, the prevalence of dyspnea was similar for male former and current smokers, and findings were similar among females. Furthermore, female former smokers had higher rates for dyspnea than males but lower rates for all other respiratory variables assessed.

Schenker, Samet, and Speizer (1982) evaluated the effect of smoking status on respiratory symptoms of 5,686 women. Age-adjusted prevalence rates for chronic cough, chronic phlegm, and wheeze most days or nights among former smokers were between those for current and never smokers. Grade 3 dyspnea was reported more often by former smokers than current smokers of 1 to 24 cigarettes per day or by never smokers.

Several reports have addressed the occurrence of symptoms in an epidemiologic study in Tucson, AZ (Lebowitz and Burrows 1977; Paoletti et al. 1985). Cross-sectional analyses, based on the first survey of the population, indicated that former smokers had a higher prevalence of chronic phlegm production than did never smokers
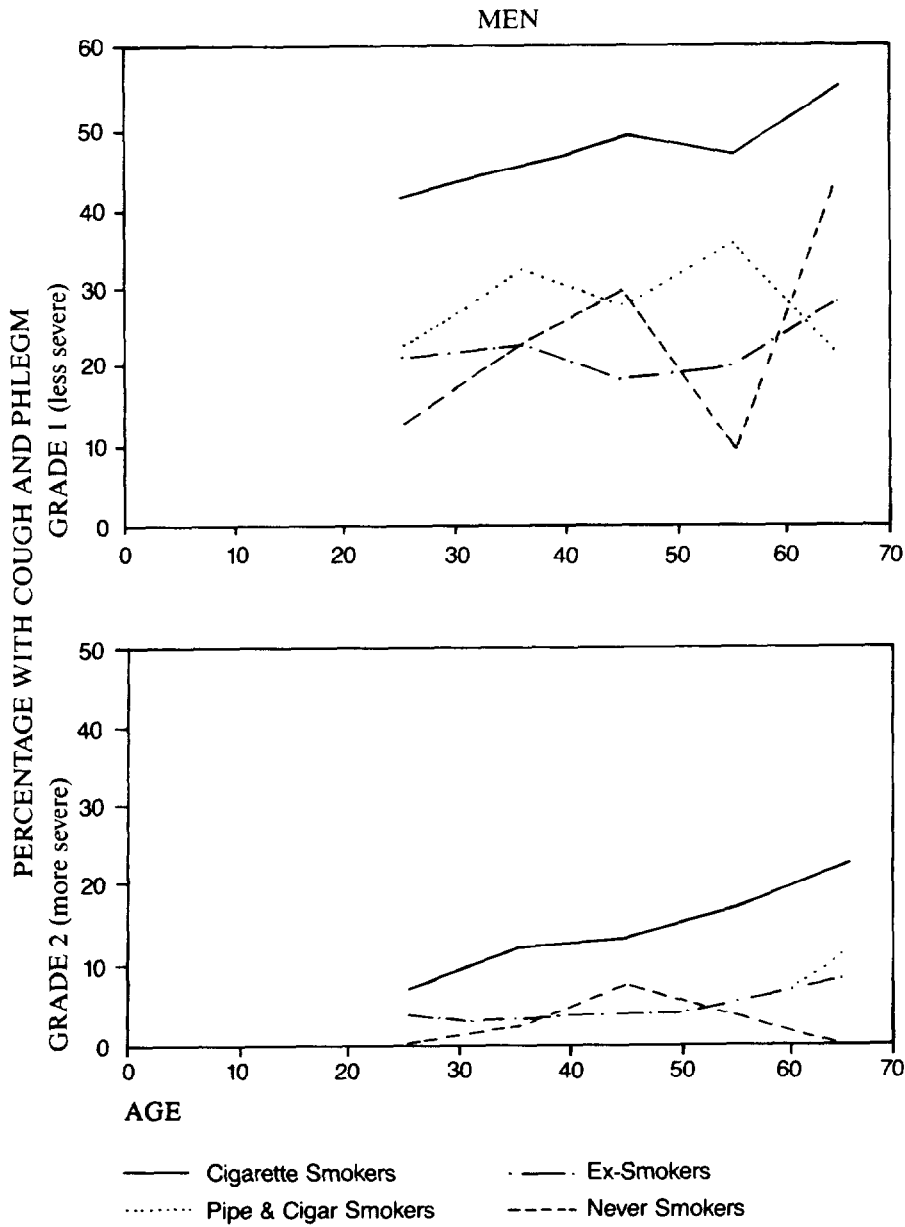
MEN

FIGURE 5.—Prevalence of cough and phlegm by smoking group

NOTE: Persons with grade 2 cough and phlegm had both symptoms and at least one symptom for ≥3 mo/yr.

SOURCE: Payne and Kjelsberg(1964).
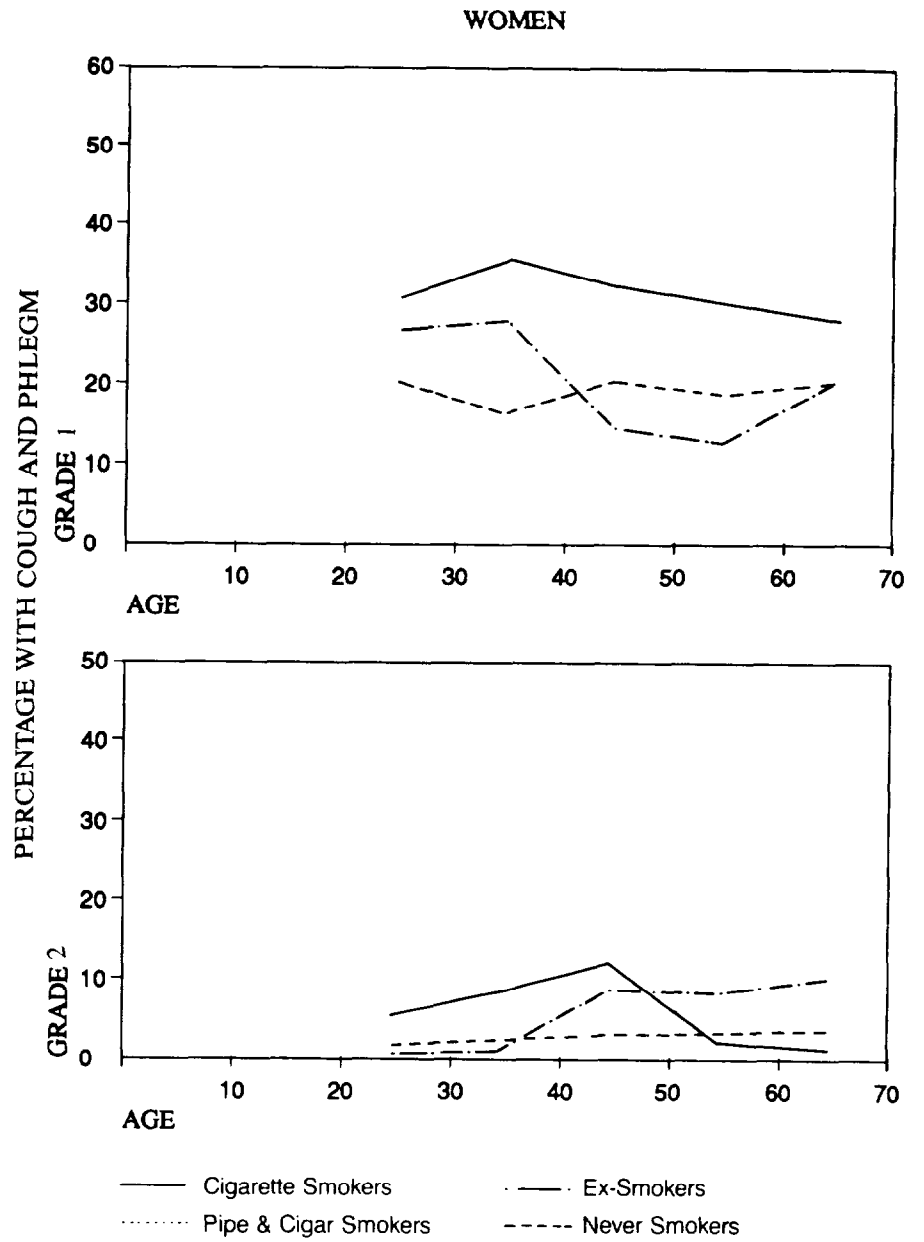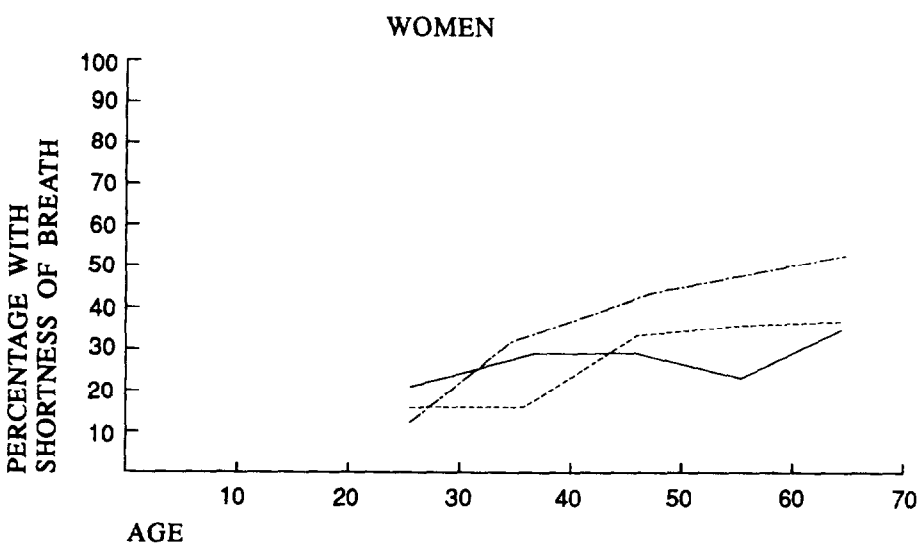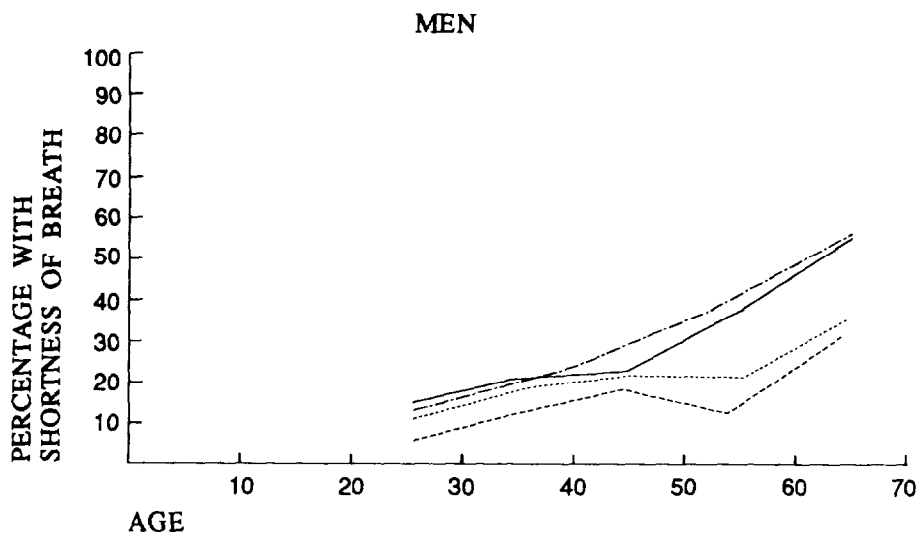
WOMEN

FIGURE 5. (Continued)—Prevalence of cough and phlegm by smoking group

NOTE: Persons with grade 2 cough and phlegm had both symptoms and at least one symptom for ≥3 mo/yr.

SOURCE: Payne and Kjelsberg(1964).

MEN

WOMEN

———— Cigarette Smokers   —··—··— Ex-Smokers
·········· Pipe & Cigar Smokers   ----------- Never Smokers

FIGURE 6.—Prevalence of dyspnea by smoking group

but a lower prevalence compared with current smokers (Table 1). When examined within age groups, the prevalence of chronic phlegm tended to be higher among older male former smokers with substantial past consumption of cigarettes, suggesting that symptoms may not revert quickly to those of never smokers.

To evaluate the effect of cumulative tar consumption on respiratory symptoms and lung function in the Tucson population, Paoletti and coworkers (1985) studied the predictive value of estimated tar exposure and pack-years on respiratory symptoms of 582 current smokers and 621 former smokers. Tar exposure was calculated from the Federal Trade Commission data on tar yield of each type of cigarette smoked and was used to classify retrospectively the smokers' exposures into categories of low and high tar pack-years as well as total tar (kilograms). Only current and former smokers with consistent consumption behavior were analyzed. Ex-smokers had lower prevalence rates of cough, chronic cough, phlegm, and chronic phlegm than did current smokers. Multiple logistic regression analysis was used to determine risk factors for any cough, any wheeze, and dyspnea. Statistical models for former smokers could not be derived using total pack-years, total tar estimates, age, or deep inhalation that significantly predicted respiratory symptoms among former smokers of either sex. The low prevalence rates of symptoms among former smokers may have limited the modeling.

Ballal (1984) analyzed the effect of depth of inhalation on respiratory symptoms in 75 former smokers as part of a larger study of the smoking behavior of 753 Sudanese medical practitioners. The proportion of former smokers complaining of any wheeze increased with degree of inhalation (slightly, moderately, or deeply), but the trend was not statistically significant. Small numbers and subject selection restrict the importance of this finding.

In summary, cross-sectional population-based studies have generally shown that former smokers have reduced prevalence rates for cough, phlegm production, and wheezing compared with current smokers. Dyspnea may not completely reverse after cessation as shown by the comparable prevalence rates for current and ex-smokers in several studies. However, dyspnea may prompt cessation when sustained smoking has caused significant physiologic impairment. Differences in symptom rates by gender have been documented in former smokers; potential explanations include sex-specific differences in reporting, differences in smoking practices, or distinct underlying physiologic responses to cessation by gender. Although the relevant data are limited, reversal of most symptoms reflecting mucous gland hypertrophy and hyperplasia and airways inflammation appears to be rapid and not dependent on cumulative smoking at the time of cessation. Measures of past cigarette consumption have not been associated with current respiratory symptoms among former smokers.

Occupational Groups

Studies of grain elevator workers, dairy farmers, cedar mill workers, and persons exposed to dust, gas, fumes, and asbestos have addressed the influence of occupation and smoking on respiratory symptoms (Table 2). Broder and coworkers (1979) and Dopico and colleagues (1984) compared respiratory symptoms in grain handlers with those of civic outside workers and of city workers, respectively. In both studies, former

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TABLE 2.—Percentages of subjects in cross-sectional occupational surveys with respiratory symptoms by smoking and occupational exposure status

Symptoms[a] Reference	Mean age (Total)	Current smokers Occupationally exposed	Control	Former smokers Occupationally exposed	Control	Never smokers Occupationally exposed	Control
Cough 3 mo/yr							
Broder et al. (1979)[b]	Grain elevator workers (A) 39±13 (189)	67.0	—	38.0	—	23.0	—
	Grain elevator workers (B) 41±13 (252)	59.0	—	23.0	—	15.0	—
	Civic outside workers (B) 42±14 (180)	—	56.0	—	15.0	—	5.0
Chan-Yeung et al. (1984)	White cedar mill workers 44.3±14.1 (511)	30.7	—	12.3	—	8.5	—
	Nonwhite cedar mill workers 39.6±9.1 (141)	30.7	—	12.3	—	8.5	—
	White office workers 43.2±11.5 (394)	—	21.8	—	3.0	—	3.5
	Nonwhite office workers 39.0±9.9 (46)	—	21.8	—	3.0	—	3.5
Kilburn, Warshaw, Thornton (1986)	Shipyard workers 58 (288)	55.0	—	33.0	—	33.0	—
	Michigan men 42 (594)	51.0	48.0	30.0	13.0	15.0	3.0
Phlegm 3 mo/yr							
Broder et al. (1979)[c]		45.0	—	17.0	—	15.0	—
Dopico et al. (1984)[d]	Grain handlers 41.0±12.0 (310)	42.0	—	32.0	—	37.0	—
	City workers 41.0±12.0 (239)	—	26.0	—	4.0	—	8.0

TABLE 2.—Continued

Symptoms[a] Reference	Mean age (Total)	Current smokers		Former smokers		Never smokers	
		Occupationally exposed	Control	Occupationally exposed	Control	Occupationally exposed	Control
Babbott et al. (1980)[e,f]	Dairy farmers (198)	39.0	—	19.0[g]	—	16.0	—
	Industry workers (516)	—	30.0	—	9.0[g]	—	10.0
Chan-Yeung et al. (1984)		26.1	21.8	14.1	8.2	10.0	7.5
Kilburn, Warshaw, Thornton (1986)		55.0	28.0	39.0	15.0	38.0	7.0
Dyspnea > grade 2							
Broder et al. (1979)[h]		23.0	21.0	12.0	11.0	15.0	5.0
		15.0	—	16.0	—	5.0	—
Dopico et al. (1984)[i]		72.0	3.0	58.0	6.0	57.0	2.0
Babbott et al. (1980)[j]		45.0	36.0	51.0[g]	34.0[g]	27.0	19.0
Chan-Yeung et al. (1984)		34.9	21.1	26.4	10.4	18.1	6.4
Kilburn, Warshaw, Thornton (1986)[j]		65.0	7.0	59.0	6.0	54.0	2.0
Wheeze							
Broder et al. (1979)[k]		5.0	4.0	8.0	6.0	4.0	8.0
		3.0	—	7.0	—	3.0	—
Dopico et al. (1984)[l]		22.0	50.0	17.0	41.0	17.0	30.0
Babbott et al. (1980)[f,l]		47.0	45.0	41.0[g]	29.0[g]	31.0	22.0
Chan-Yeung et al. (1984)[m]		23.4	24.8	12.3	7.5	9.2	7.5
Kilburn, Warshaw, Thornton (1986)[l]		68.0	13.0	43.0	8.0	32.0	1.0

[a]Males only; symptoms not mutually exclusive.
[b]Cough for more than a few days/wk.
[c]Phlegm for more than a few days/wk.
[d]Morning expectoration.
[e]Chronic sputum production; sputum most days persisting for at least 3 mo/yr.
[f]Matched on age and cigarette smoking (current, farm: industry 35.59 vs. 35.41; former, 43.20 vs. 43.24; never, 34.01 vs. 33.88).
[g]Matched on years since cessation, farmers 7.95 vs. industry 8.43.
[h]Shortness of breath.
[i]Grade 2 dyspnea.
[j]Dyspnea at two flights of stairs.
[k]Wheeze in attacks.
[l]Ever wheeze.
[m]Persistant wheeze; wheeze with colds or wheeze on most days or nights.

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smokers had intermediate prevalence rates for cough, sputum production, wheeze, and shortness of breath compared with current and never smokers. Additionally, former smokers who were grain handlers had more acute and chronic symptoms than ex-smokers who were outside civil or city workers. For grain workers, length of employment had no effect on the prevalence of respiratory symptoms within each smoking group. The results of these two studies differ in that the occupational effect was minimal and less than the smoking effect in the former investigation but significant and greater in the latter. The choice of control subjects may explain this discrepancy.

Babbott and colleagues (1980) assessed the respiratory symptoms of 198 Vermont dairy farmers and 516 nonmineral industrial workers. Former smokers were matched on age (mean 43 years) and years since cessation (mean 8 years). Chronic sputum production, wheezing, and dyspnea were more common among current smokers than among former or never smokers and more frequent among dairy farmers than industrial workers. Similar results were found by Chan-Yeung and coworkers (1984) in a study of 652 cedar mill workers and 440 control office workers. Korn and associates (1987), in a population sample of 8,515 white adults, showed that smoking and exposure to dust, gases, or fumes were independently associated with an increased prevalence of chronic cough, chronic phlegm, persistent wheeze, and breathlessness. Former smokers with gas or fume exposure were more likely to have respiratory symptoms, particularly breathlessness, than exposed current or never smokers. A multiplicative relationship between smoking and occupational exposure was found for breathlessness but not for other symptoms.

Kilburn, Warshaw, and Thornton (1986) conducted an investigation of respiratory symptoms, cardiopulmonary diseases, and asbestosis among 338 male and 81 female shipyard workers and their families. In general, the study group had more symptoms than reported from a similarly stratified random sample of the Michigan population (Miller et al. 1988). The authors suggested that environmental influences in the Los Angeles area may explain the higher rates. Male shipyard workers who were former smokers had more cough, sputum production, and wheezing than shipyard workers who were current smokers, whereas the pattern was reversed for female shipyard workers.

In summary, results from selected occupational groups support the findings from the community-based studies, although work exposures may interact with smoking in determining the occurrence of symptoms among former smokers (US DHHS 1985). The results of these investigations may be affected by misclassification of exposures and by selection or recall bias. As in the community-based studies, limited descriptive information is provided on former smokers.

Longitudinal Studies

Numerous longitudinal population-based studies have found rapid resolution of most respiratory symptoms after smoking cessation (Table 3). A study by Woolf and Zamel (1980) indicated that 302 female former smokers with a mean cigarette consumption of 15 pack-years had dramatic resolution of respiratory symptoms within 5 years. These investigators defined former smokers as women who had not smoked for at least 1 year before entry into the study. Persistent former and never smokers were comparable in

TABLE 3.—Change (%) in presence of respiratory symptoms, longitudinal studies, by cigarette smoking status

Symptoms Reference	Age (mean)	Continuing smokers			Former smokers			Never smokers		
		Lost	No change[a]	Gained	Lost	No change[a]	Gained	Lost	No change[a]	Gained
Cough 3 mo/yr										
Woolf and Zamel (1980)[b]	Smokers Light: 43.2±1.7[c] Moderate: 39.1±1.1 Heavy: 38.6 ±0.9	18.0	66.0	16.0	2.0	85.0	13.0	5.0	86.0	9.0
Tashkin et al. (1984)[d]	Smokers Male: 45.1 Female: 46.9 Quitters Male: 43.4 Female: 45.6	8.3	77.6	14.1	14.3	82.7	3.0	—	—	—
Comstock et al. (1970)[e]	40–59	Net change: 1.0			Net change: −21.0			Net change: 3.0		
Sharp et al. (1973)[f,g]	43–58	10.7	78.0	11.3	16.7	78.5	4.8	4.5	90.8	4.7
Friedman and Siegelaub (1980)[g]	20–79									
	White male ≥1 ppd[h]	7.6	85.5	6.9	10.1	89.3	0.6	—	—	
	White female ≥1 ppd	7.4	85.2	7.4	5.0	92.5	2.5	—	—	...
	Black male ≥1 ppd	5.5	89.2	5.3	1.3	97.4	1.3	—	—	—
	Black female ≥1 ppd	5.0	89.7	5.3	2.9	96.6	1.5	—	—	—
Phlegm 3 mo/yr										
Tashkin et al. (1984)		8.8	77.9	13.3	7.7	86.3	6.0	—	—	—