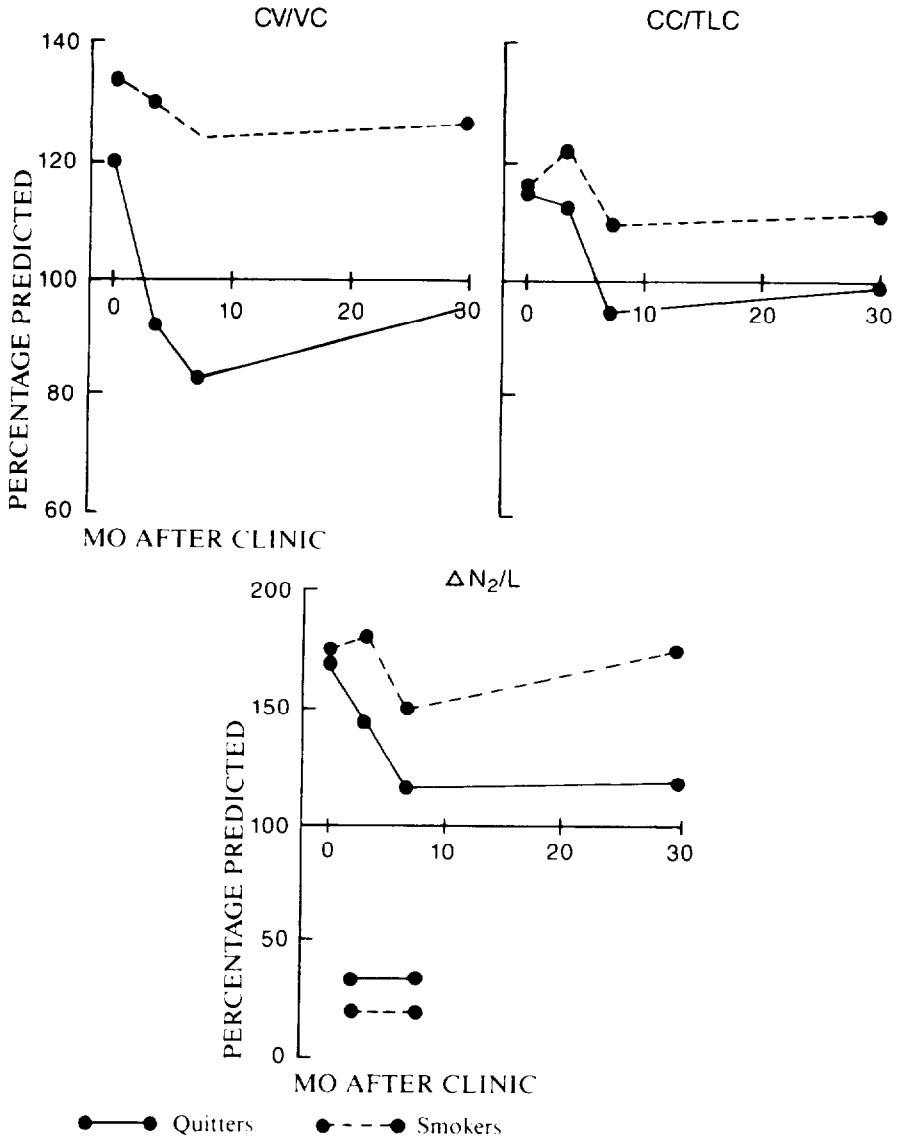

FIGURE 9.—Mean values for the ratio of CV/VC, of CC/TLC, and slope for phase III of the single breath N_2 test ($\Delta N_2/L$), expressed as a percentage of predicted values in 15 quitters and 42 smokers during 30 months after 2 smoking cessation clinics

NOTE: Asterisks (*) denote a significant difference from the initial value at $p<0.05$. CV=closing volume; VC=vital capacity; CC=closing capacity; TLC=total lung capacity.

SOURCE: Buist, Nagy, Sexton (1979).

small improvements in CV and CC were observed, although slope of phase III improved by 10 percent.

Martin and coworkers (1975) stated that "CV did not improve with cessation" among 12 participants in a smoking cessation program tracked for 1 to 3 months. In a 4-year followup of eight men who successfully gave up smoking, Pride and colleagues (1980) reported no improvement in CV, but a significant decline in the slope of phase III within the first few months of cessation. Further improvement did not occur over subsequent years.

In summary, abnormalities in the small airways, as measured by CV, CC, and slope of phase III, are substantially reversible among smokers who have not developed significant airflow obstruction. Recovery occurs rapidly and appears to be complete for these measures between 6 months and 1 year after cessation, although the implications of these changes for morbidity and mortality are uncertain.

Abnormal frequency dependence of lung compliance (an increased reduction of lung compliance as respiratory frequency increases) also indicates abnormal function of the small airways. Ingram and O'Cain (1971) examined six smokers with abnormal frequency dependence of compliance who quit smoking. At 1 to 8 weeks after cessation, values in all six had returned to normal. Martin and coworkers (1975) studied 12 participants in a smoking cessation program. At 1 to 3 months after cessation, dynamic compliance was less frequency dependent among 8 of the 12 subjects. Zamel, Leroux, and Ramcharan (1979) also reported less frequency dependence of dynamic compliance among 26 healthy smokers at 2 months after cessation.

Diffusing Capacity Among Former Smokers

Numerous studies, using a variety of methods, have shown that pulmonary diffusing capacity is between 6 and 20 percent lower among smokers than among age-matched nonsmokers (Teculescu and Stanescu 1970; Van Ganse, Ferris, Cotes 1972; Krumholz and Hedrick 1973; Frans et al. 1975; Hyland et al. 1978; Enjeti et al. 1978; Bosisio et al. 1980; Miller et al. 1983; Knudson et al. 1984). Only a few studies, however, have assessed the effect of smoking cessation on diffusing capacity.

Marcq and Minette (1976) measured single breath carbon monoxide (CO) diffusing capacity ($DL_{CO}SB$) in male subjects with normal values of FEV_1 and FEV_1 divided by FVC. Diffusing capacity was below normal in 13 of 54 (24 percent) of the current smokers compared with 1 of 17 (6 percent) of the former smokers of at least 6 months abstinence.

Miller and colleagues (1983) examined $DL_{CO}SB$ in a survey of 511 randomly selected subjects from a population in Michigan. Among never smokers, the mean $DL_{CO}SB$ was 32.5 mL CO per mm Hg per minute for males and 23.0 mL CO per mm Hg per minute for females. Compared with never smokers and adjusted for age and height, male current smokers had 17 percent lower (5.4 mL CO/mm Hg per minute), and female current smokers had 16 percent lower (3.6 mL CO/mm Hg per minute) $DL_{CO}SB$. Male former smokers abstinent for at least 2 years were lower by 7 percent (2.3 mL CO/mm Hg per minute) compared with never smokers, whereas no difference was found between female current and former smokers.

Zamel, Leroux, and Ramcharan (1979) measured $DL_{CO}SB$ among 26 healthy smokers before and 2 months after cessation. Although $DL_{CO}SB$ improved slightly following cessation (0.8 mL CO/mm Hg per minute), the difference was not statistically significant.

Knudson, Kaltenborn, and Burrows (1989) measured $DL_{CO}SB$ in the seventh population survey conducted in the longitudinal study of a population-based sample in Tucson, AZ. Among current and former smokers, $DL_{CO}SB$ dropped as cumulative consumption of cigarettes increased (Figure 10). Current smokers had significantly lower $DL_{CO}SB$ than either former smokers or never smokers; in persons with normal spirometry, former and never smokers had comparable $DL_{CO}SB$; former smokers in the group with abnormal spirometry had significantly lower $DL_{CO}SB$. The $DL_{CO}SB$ quickly returned to normal as the duration of abstinence increased. Within 2 years of quitting, $DL_{CO}SB$ had reached 100 percent of that predicted for women; after 3 years of abstinence, mean $DL_{CO}SB$ was 100 percent of that predicted for men.

These data suggest that the effects of cigarette smoking on pulmonary diffusing capacity, as on other measures of lung function, include both irreversible and reversible components. The extent of irreversible change is predicted by cumulative consumption; the reversible component improves quickly after cessation.

Other Measures

Among 19 heavy smokers studied by Dirksen, Janzon, and Lindell (1974), ventilation distribution measured by open-circuit nitrogen clearance improved 1 week after smoking cessation. Regional lung function measured with ^{133}Xe showed improvement 1 to 3 months after cessation in the study by Martin and colleagues (1975). Zamel and Webster (1984) performed detailed studies of five men and five women before and 60 days after cessation. Although $\dot{V}_{max60percent\ TLC}$ with helium and air and the maximum flow-static recoil curve did not change, static recoil pressure at 60 percent TLC did decrease significantly 2 months after cessation in 18 of 22 smokers. Michaels and coworkers (1979) also observed a decrease in static recoil pressure at any lung volume after smoking cessation. These authors concluded that a decrease in small airway muscle tone might have accounted for these findings.

Longitudinal Population-Based Studies

The natural history of COPD has been described in longitudinal studies of up to two decades. Although a population has not been studied from childhood to the development of COPD during adulthood, the available data from existing separate investigations encompass the entire course of the disease and support the conceptual model presented earlier (Figure 2).

Measures of pulmonary function begin to decline after 25 to 30 years of age. For FEV_1, the annual rate of decline, as estimated from cross-sectional studies, is about 20 to 30 mL annually (US DHHS 1984). Faster loss of function over a sufficient period of time can lead to the development of clinically significant airflow obstruction (Figure 2). The available longitudinal data indicate that cigarette smoking is the primary risk

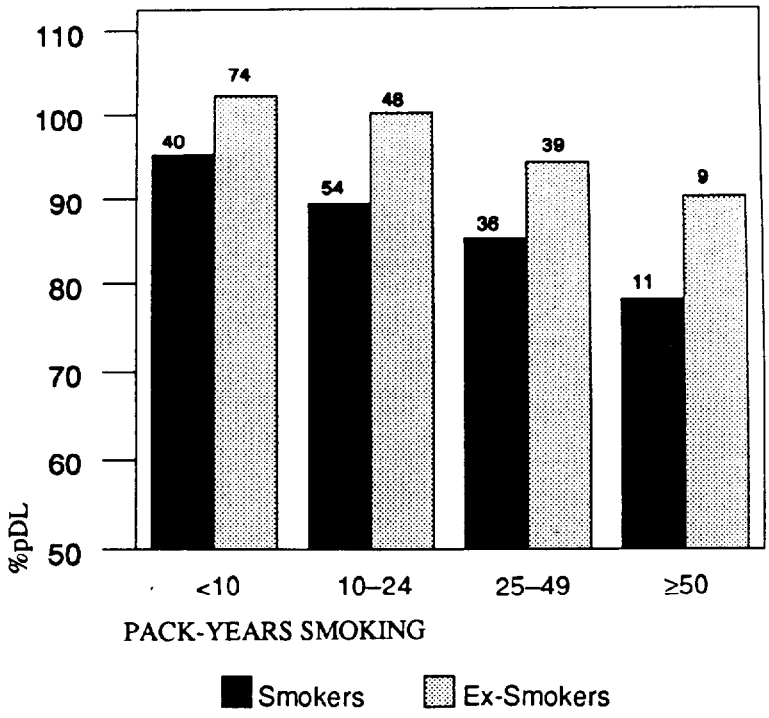

FIGURE 10.—Percent-predicted diffusing capacity (%pDL) by pack-years of smoking, current smokers and former smokers, in a study of adults in Tucson, AZ

NOTE: Numbers above bars represent sample sizes.

SOURCE: Knudson, Kaltenborn, Burrows (1989).

factor for excessive loss of FEV_1 (US DHHS 1984), and smokers have much faster rates of loss of FEV_1 than never smokers (Table 9). Table 9 describes rates of change in lung function in selected major longitudinal studies. In each, former smokers or quitters have less decline than current smokers during the followup period.

In many investigations, dose–response relationships have been found between the amount smoked during the followup interval and the rate of the FEV_1 decline (US DHHS 1984). For example, Fletcher and colleagues (1976) conducted a study of 792 employed men and performed pulmonary function measurements semiannually for 8 years. They reported that the annual loss of FEV_1 was 36 mL per year for never smokers. The rate of decline among cigarette smokers increased with amount smoked per day (44 mL/year for ≤4 cigarettes/day; 46 mL/year for 5 to 15 cigarettes/day; 54 mL/year for 15 to 25 cigarettes/day; and 54 mL/year for >25 cigarettes/day). The rate

TABLE 9.—Population-based longitudinal studies of annual decline in pulmonary function

Reference	Population	Followup	Gender	Measure	Rate of decline by smoking status			
					Never smokers	Former smokers	Quitters	Smokers
Wilhelmsen, Orha, Tibblin (1969)	Swedish men born in 1913	4 yr	Male	VC (mL/yr)	63	58	58	94
				FEV_1 (mL/yr)	43	33	40	70
				PEF (L/min/yr)	128	140	100	155
Ashley et al. (1975)	Framingham Study	10 yr 2 exams	Male	FVC (mL/yr)	39		46	58
				FEV_1/FVC (%/yr)	0.3		-0.1	0.5
			Female	FVC (mL/yr)	33		30	39
				FEV_1/FVC (%/yr)	4.2		0.2	3.0
Fletcher et al. (1976)	British workers	8 yr Semiannual	Male	FEV_1 (mL/yr)	36	31	38	50
Kauffmann et al. (1979)	French workers	12 yr	Male	FEV_1 (mL/yr)[a]	42	44		49
Huhti and Ikkala (1980)	Middle-aged rural Finns	10 yr	Male	FEV_1 (mL/yr)	33	45	44	51
			Female	FEV_1 (mL/yr)	27	27	39	35
Woolf and Zamel (1980)	Canadian volunteers aged 25-54	5 yr 2 exams	Female	FEV_1 (%/yr)	0.3	0.2		0.7
				FEV_1/FVC (%/yr)	1.3	1.4		1.7
Bossé et al. (1980)	Healthy US veterans	10 yr 3 exams	Male	FEV_1 (mL/yr)	52	57		62
				FVC (mL/yr)	69	72		73

TABLE 9.—Continued

Reference	Population	Followup	Gender	Measure	Rate of decline by smoking status			
					Never smokers	Former smokers	Quitters	Smokers
Bossé et al. (1981)	Healthy US veterans	5 yr 2 exams	Male	FEV_1 (mL/yr)[b] FVC (mL/yr)[b]	61 68		49 64	78 91
Van der Lende et al. (1981)	Random sample in the Netherlands, aged 15–39	9–13 yr 4 exams	Male and Female	FEV_1 (mL/yr)[c] VC (mL/yr)[c]	16.6 13.7	13.4 13.2		24.5 15.7
Tashkin et al. (1984)	Population sample in southern California	5 yr 2 exams	Male	FEV_1 (mL/yr)[d] FVC (mL/yr)[d]	56 60	52 60	62 68	70 64
			Female	FEV_1 (mL/yr) FVC (mL/yr)	42 44	38 42	38 44	54 54
Taylor et al. (1985)	Volunteer population in the United Kingdom	7.5 yr 2 exams	Male	FEV_1/H^3 (mL/yr/m^3)	6.6	8.0[e]		10.9

TABLE 9.—Continued

Reference	Population	Followup	Gender	Measure	Rate of decline by smoking status			
					Never smokers	Former smokers	Quitters	Smokers
Camilli et al. (1987)	Population sample in Tucson, AZ	Mean 9.4 yr 5.2 exams	Male	FEV_1 (mL/yr)[f]	12.9	10.8	13.2	25.8
			Female	FEV_1 (mL/yr)[g]	7.6	6.5	2.9	14.6
Burrows et al. (1987)	Population sample in Tucson, AZ	10.0 yr 5.4 exams	Male	FEV_1 (mL/yr)[h]		11.8		26.6
Townsend et al. (in press)	MRFIT	2–4 yr	Male	FEV_1 (mL/yr)	51	44	50	59

NOTE: Negative numbers indicate an increase. Former smokers stopped smoking prior to start of study; quitters stopped smoking after start of study. Mean values for all smokers have been calculated weighted by number of subjects, where published data was stratified by amount of smoking. VC=vital capacity; FEV_1=1-sec forced expiratory volume; PEF=peak expiratory flow; FVC=forced vital capacity; H^3=height cubed; MRFIT=Multiple Risk Factor Intervention Trial.

[a]Adjusted for initial level.

[b]Adjusted for age.

[c]Adjusted for initial level, height, sex, and area of residence. Weighted mean for smokers.

[d]Adjusted for age, height, and area of residence.

[e]Includes former smokers and quitters.

[f]Adjusted to age 50, height 172 cm.

[g]Adjusted to age 50, height 161 cm.

[h]Recalculated from FEV_1/FVC specific values.

of loss among former smokers (i.e., smokers who stopped before the first examination) was 31 mL per year, not significantly different from that of never smokers. In addition, smokers who stopped in the first 2 years of the followup had an annual decline of 38 mL per year. The authors concluded that smokers who stopped before or early in the study had FEV_1 declines similar to never smokers. In spite of FEV_1 levels having been reduced by previous smoking, further damage to FEV_1 due to smoking ceases within a few years of cessation. However, recovery of function was not documented in the study of Fletcher and colleagues (1976). These results have been confirmed in multiple population-based longitudinal studies of FEV_1 and other pulmonary function parameters (Table 9).

Camilli and associates (1987) examined longitudinal decline of FEV_1 in a population sample of 1,705 adults in Tucson, AZ. Mean followup was 9.4 years with an average of 5.2 examinations. Former smokers were defined as having stopped before enrollment and continuing to abstain at their last two followup examinations. Quitters smoked on entry into the program but stopped before their last two followup examinations. Rates of loss for former smokers and quitters were comparable with those for never smokers and less than those for smokers (Table 9). The age-specific rates of loss (Figure 11) suggest that the benefits of cessation may be greatest among the youngest smokers, that is those with the shortest smoking history. FEV_1 increased in the youngest group, a finding that the authors interpreted as indicating that the earliest effects of smoking are relatively reversible and could represent, in part, a bronchoconstrictive effect.

Among the males in the 50- to 69-year-old age group (Figure 12), 10 of the 24 subjects who quit did so before their second followup examination. For these 10 subjects, the revised annual loss of FEV_1 from the time of cessation returned to that of never smokers, and was much less than that among smokers. In several years, reduced lung function due to previous smoking was not recovered, except possibly among former smokers who had only been smoking a short time.

Taylor, Joyce, and coworkers (1985) examined the annual decline of height-corrected FEV_1 (FEV_1 divided by height^3) over 7.5 years in 227 men who were free of a clinical diagnosis of asthma and had not received bronchodilator treatment. Former smokers had an annual decline of FEV_1 divided by height^3 (8.0 ± 0.8 mL/year/m^3) that was not statistically different from that of never smokers (6.6 ± 0.6 mL/year/m^3) but was significantly less than that of continuing smokers (10.9 ± 0.7 mL/year/m^3). The 71 former smokers included 50 smokers who had stopped during the followup period. Smokers with bronchial reactivity to inhaled histamine had significantly accelerated annual decline of FEV_1, but an effect of bronchial reactivity was not found among former smokers or never smokers. The reactive former smokers had a lower level percent-predicted FEV_1 at the end of the followup (96.4 vs. 111.4 percent predicted). Because their annual rate of loss was not accelerated, the low level of former smokers must be attributed to either steeper decline while they were smoking, low level of FEV_1 before they started smoking, or both.

Townsend and colleagues (in press) have recently reported on FEV_1 decline in participants in the Multiple Risk Factor Intervention Trial. The analysis was limited to 4,926 subjects who had not used β-blocking agents or smoked cigars, cigarillos, or pipes

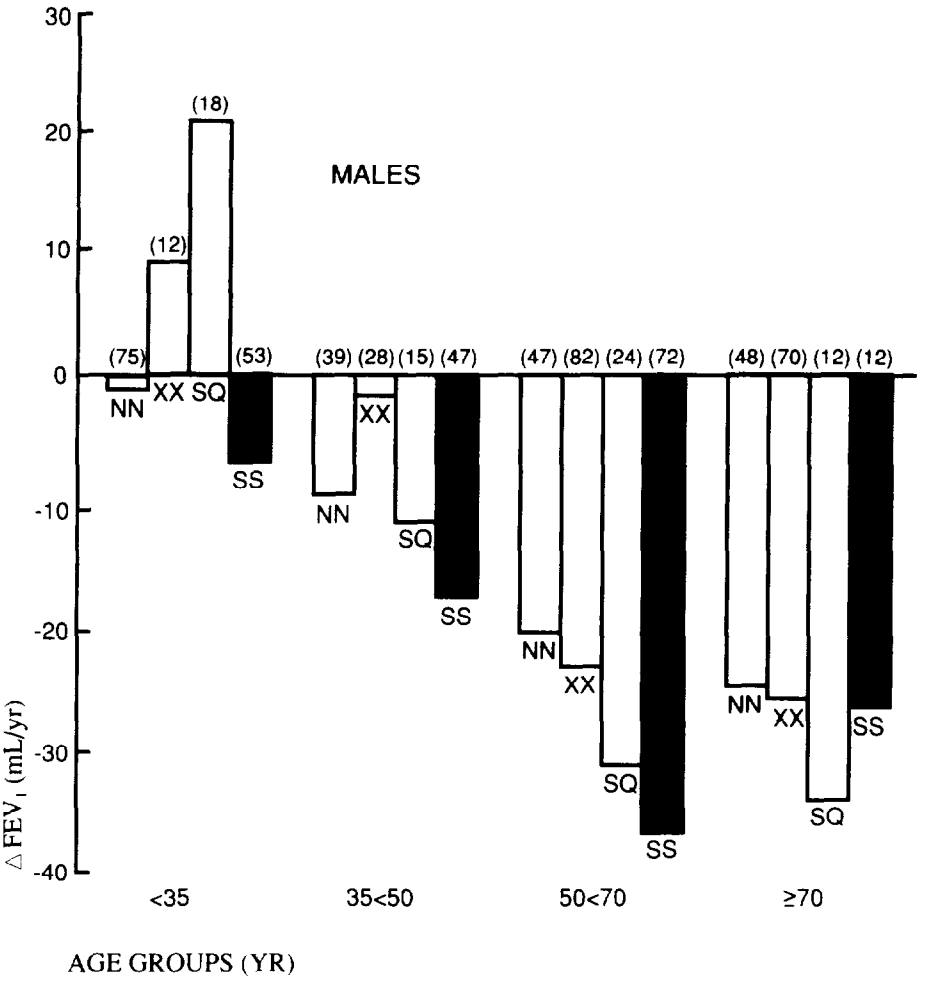

FIGURE 11.—Mean ΔFEV_1 values in never smokers (NN), consistent ex-smokers (XX), subjects who quit smoking during followup (SQ), and consistent smokers (SS) in several age groups

NOTE: Numbers of subjects in each category are shown in parentheses. FEV_1=1-sec forced expiratory volume.

SOURCE: Camilli et al. (1987)

during the trial and who were observed over 2 to 4 years during the latter half of the study. Subjects who quit smoking during the first 12 months of the study lost FEV_1 at a significantly lower rate than those reporting smoking throughout the trial. Cross-sectional analysis of data from the midpoint of the trial indicated the highest level of FEV_1 for never smokers and the lowest levels for continuing smokers at all ages; FEV_1 levels for former smokers at enrollment and those quitting during the first year were inter-

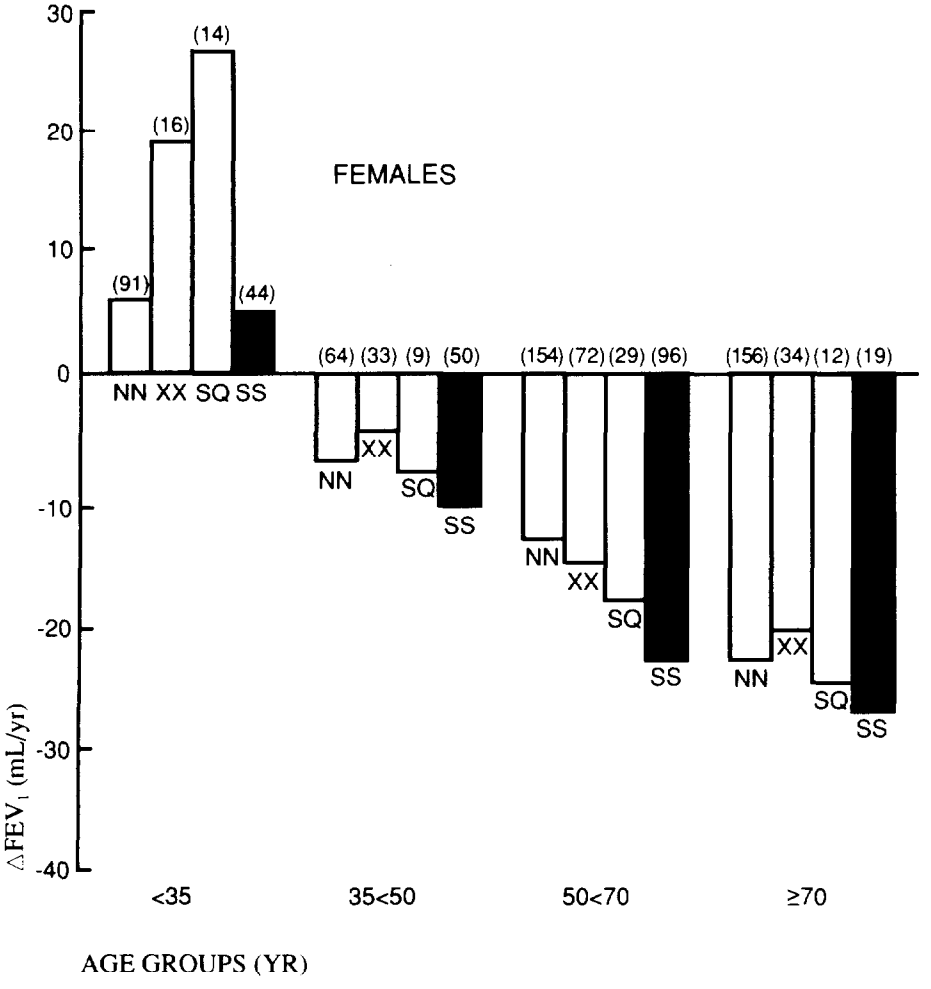

FIGURE 11. (Continued)—Mean ΔFEV_1 values in never smokers (NN), consistent ex-smokers (XX), subjects who quit smoking during followup (SQ), and consistent smokers (SS) in several age groups

NOTE: Numbers of subjects in each category are shown in parentheses. FEV_1=1-sec forced expiratory volume.

SOURCE: Camilli et al. (1987)

mediate. The findings in the group quitting smoking during the first 12 months may underestimate the benefits of cessation because of subsequent relapse within this group: 16 percent of the quitters had an elevated serum thiocyanate level (>100 μm/dL) indicative of smoking at the first examination compared with 6 percent of never smokers and 7 percent of former smokers.

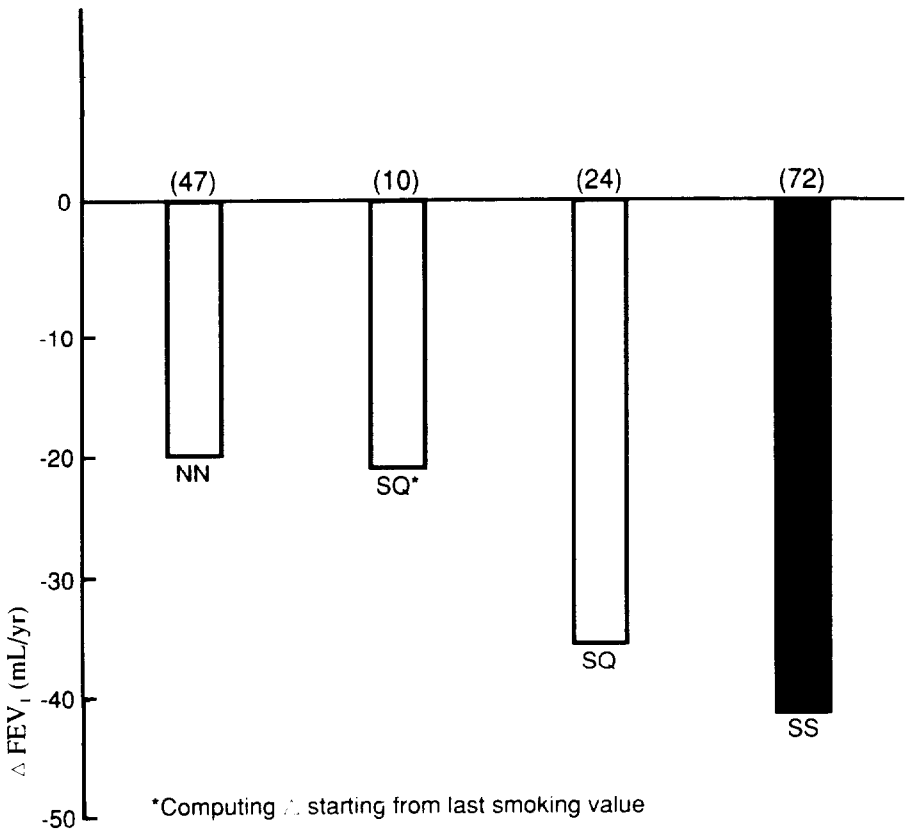

FIGURE 12.—Effects of quitting smoking during followup among men aged 50–69

NOTE: Subjects in the SQ* group are included in the SQ group.

SOURCE: Camilli et al. (1987).

In the Copenhagen City Heart Study, spirometry was performed on 2 occasions separated by 5 years for 12,698 adult residents of the city selected at random (Lange et al. 1989). In general, persons who stopped smoking during this interval experienced less decline of FEV_1 than those who continued to smoke (Table 10); the effect of cessation varied with subject age and amount smoked at the time of quitting.

In 1986, the National Heart, Lung, and Blood Institute (NHLBI) initiated a multicenter investigation, the Lung Health Study, to determine whether smoking cessation and bronchodilator therapy can influence the course of subjects without clinical illness who are at high risk for the development of COPD (Anthonisen 1989). Six thousand smokers, aged 35 to 59 years, with evidence of airways obstruction were recruited. They were randomly assigned to one of three groups: a group that received no intervention or usual care group; a group that received an intensive state-of-the-art

TABLE 10.— Decline of FEV_1 (mL/yr) in subjects in the Copenhagen City Heart Study

Smoking group	Women		Men	
	<55 yr	≥55 yr	<55 yr	≥55 yr
Never smokers	13 (722)	32 (754)	21 (302)	34 (151)
Former smokers	18 (321)	32 (307)	27 (306)	36 (430)
Continuing light smokers	17 (641)	39 (439)	22 (279)	52 (227)
Quitting light smokers	15 (80)	28 (77)	17 (51)	11 (31)
Continuing heavy smokers	30 (624)	48 (196)	42 (634)	56 (248)
Quitting heavy smokers	9 (17)	— (8)	36 (32)	43 (14)

NOTE: Numbers of subjects given in parentheses. Light smokers consumed <15 cig/day; heavy smokers consumed ≥15 cig/day. FEV =1-sec forced expiratory volume.

SOURCE: Abstracted from table 2 in Lange et al. (1989).

smoking cessation program and regular therapy with an inhaled bronchodilator (ipratropium bromide); and a third group that received the smoking cessation program and a placebo bronchodilator. Placebo/bronchodilator therapy was administered in double-blind fashion. All groups were studied at yearly intervals for 5 years, with rate of change of FEV_1 as the primary end point and respiratory morbidity as a secondary end-point.

In this investigation, a large number of smokers with early airways obstruction were characterized and will be studied closely for 5 years. An extensive data base will be created to test numerous hypotheses regarding smoking cessation. The question of airways reactivity as a risk factor for rapid lung function loss will be tested definitively in that methacholine sensitivity will have been measured both at the beginning and at the followup period.

The findings of the longitudinal studies on smoking cessation and decline of FEV_1 have important implications. Persons losing FEV_1 at a greater rate are at risk of developing COPD. After cessation, the return of the rate of decline of FEV_1 to that of never smokers implies that the process leading to COPD can be arrested by cessation.

PART III. AIRWAY RESPONSIVENESS, CIGARETTE SMOKING, AND SMOKING CESSATION

Population-based studies support a role for smoking as a cause of heightened airway responsiveness (Woolcock et al. 1987; Sparrow et al. 1987; Burney et al. 1987). Most cross-sectional studies that have evaluated this relationship have not adjusted for baseline airway caliber, which may be reduced among smokers (Woolcock et al. 1987; Burney et al. 1987; Welty et al. 1984; Van der Lende et al. 1981; Pham et al. 1984; Buczko et al. 1984), so that it is difficult to determine how much of the increase in airway responsiveness is accounted for by a direct smoking effect or by a reduction in

prechallenge pulmonary function (Fanta and Ingram 1981). Atopy may modify the influence of smoking by further increasing nonspecific airway responsiveness. As noted by O'Connor, Sparrow, and Weiss (1989), this modification may be underestimated in most studies because those with an allergic predisposition and heightened nonspecific responsiveness may not begin smoking—or if they do begin, they may soon quit. The importance of smoking-induced heightened airway responsiveness in the pathogenesis of asthma is unknown, and airway hyperresponsiveness is a suspected risk factor for COPD.

Mechanisms of Heightened Airway Responsiveness Among Smokers and Former Smokers

In both clinical and population-based studies, smoking has been associated with increased airway epithelial permeability (Jones et al. 1980; Minty, Jordan, Jones 1981; Mason et al. 1983), elevated levels of IgE (Burrows et al. 1981; Warren et al. 1982; Zetterström et al. 1981; Hällgren et al. 1982; Bonini et al. 1982; Stein et al. 1983), and greater numbers of peripheral eosinophils (Burrows et al. 1980; Taylor, Gross et al. 1985; Tollerud et al. 1989; Kauffmann et al. 1986). These physiologic and immunologic alterations may partly explain the observed relationship between cigarette consumption and heightened airway responsiveness and/or asthma (Brown, McFadden, Ingram 1977; Malo, Filiatrault, Martin 1982; Cockcroft et al. 1979; Buczko et al. 1984; Casale et al. 1987; Van der Lende et al. 1981; Gerrard, Cockcroft et al. 1980; Kabiraj et al. 1982; Pham et al. 1984; Enarson et al. 1985; Taylor, Joyce et al. 1985; Woolcock et al. 1987; Sparrow et al. 1987; Rijcken et al. 1987; Burney et al. 1987). Allergy to environmental antigens is known to modify this relationship (Burrows, Lebowitz, Barbee 1976; Welty et al. 1984; Buczko et al. 1984; Schachter, Doyle, Beck 1984; Kiviloog, Irnell, Eklund 1974; Dodge and Burrows 1980). The complexity of these interrelationships is only partially explained by published findings, and additional clarifying studies are needed. This Section reviews studies that have addressed the above associations with respect to ex-smokers which may explain why airway responsiveness returns to normal with abstinence.

Smoking increases pulmonary epithelial permeability, which rapidly returns to normal among young smokers after cessation. Minty, Jordan, and Jones (1981) used a radiolabeled aerosol technique to study 10 young asymptomatic male smokers who had stopped smoking for 1, 3, 7, 14, and 21 days. They found that recovery of the epithelial integrity began within 24 hours and reached maximum at 7 days. Mason and colleagues (1983) later confirmed these findings in 10 young smokers. These studies included small numbers of subjects and had short followup periods after cessation, making interpretation and generalization of the findings difficult.

Cross-Sectional Studies

Cross-sectional population-based data have shown that former smokers have less airway responsiveness than current smokers. Burney and colleagues (1987) studied 511 randomly selected subjects aged 18 to 64 years using inhaled histamine challenge.

Of the population, 14 percent were histamine-responsive as defined by PD20 (the dose of histamine resulting in a 20-percent decline in FEV_1). Responsiveness was related to atopy in younger subjects (aged <40 years) and smoking in older participants (aged >40 years). Former smokers (N=116) had bronchial reactivity similar to never smokers but lower than current smokers across all age strata (12 vs. 10 vs. 24 percent, respectively). The increase in threshold dose of histamine with age for former smokers was 0.053 per year compared with 0.086 per year among current smokers and 0.027 per year among never smokers. However, for those aged 35 to 44 years, former smokers were more responsive than the other smoking groups (14 vs. 13 and 7 percent for current and never smokers, respectively). The criteria for classification of former smokers were not provided.

Cerveri and colleagues (1989) found similar results in their study of 295 normal never smokers, 70 normal current smokers, and 50 former smokers randomly selected from the general population of a small town in Lombardy, Italy. The daily amount smoked was a stronger predictor of airway responsiveness than the duration of cigarette use. Further, among ex-smokers, duration of abstinence did not significantly influence airway responsiveness; however, former smokers with longer abstinence tended to have less bronchial reactivity.

Longitudinal Studies

Longitudinal population-based studies have not been conducted specifically to evaluate temporal changes in airway responsiveness among former smokers. Several cohort studies designed to measure declines in spirometric function have included single measurements of airway reactivity. These studies generally confirmed lower responsiveness among former smokers than current smokers and suggested an association between bronchial reactivity and a more rapid decline in ventilatory function. Vollmer, Johnson, and Buist (1985) examined bronchodilator responsiveness among subjects from 2 cohorts, 351 members of the Portland Cohort, which included a random sample of 507 Multnomah County employees, and 444 adults from the Screening Center Cohort, consisting of 1,024 subjects screened for emphysema. Individuals were classified as responsive if they showed a 7.72-percent increase in FEV_1 after two puffs of an isoproterenol metered-dose inhaler. Although no data were presented, former smokers were reported to have a distribution of responsiveness similar to that of current smokers and skewed toward higher values. In case–control analysis conducted within the cohort, responsiveness in both current and former smokers was associated with lower baseline pulmonary function and more rapid ventilatory decline over 9 to 11 years. Former smokers in both cohorts had rates of decline that approximated or exceeded those for current smokers, especially among those subjects who were responsive.

In a 6-year study of 267 white male grain elevator workers, Tabona and coworkers (1984) found that the percentage of former smokers who were methacholine responsive, defined as a PC20 ≤8 mg/mL, was similar to that of never smokers (19.6 vs. 16.7 vs. 25.8 percent for former, never, and current smokers, respectively). In contrast to the Vollmer, Johnson, and Buist study (1985), former smokers showed the lowest ventilatory decline of all smoking groups across all age categories (Tabona et al. 1984).

However, former smokers who were methacholine responsive had greater FEV_1 loss over the 6 years of the study than those who were not methacholine responsive. Atopy, presence of symptoms, and initial lung function were not predictive of decline in lung function.

Finally, Taylor, Joyce, and coworkers (1985) conducted an investigation over a 7.5-year period of bronchial reactivity and FEV_1 annual rate of decline among 227 London men, aged 25 to 61 years. These investigators confirmed the results for current smokers of Vollmer, Johnson, and Buist (1985) and Tabona and coworkers (1984). Similarly, former smokers had intermediate levels of methacholine responsiveness compared with the other groups, and those former smokers who were responsive had lower rates of baseline ventilatory function. In contrast, however, former smokers had comparable rates of ventilatory decline, regardless of methacholine responsiveness.

In all of these longitudinal studies, bronchodilator or methacholine responsiveness was measured near the end of the study period. Furthermore, precise definitions of former smokers with regard to amount smoked, duration of abstinence, and reasons for quitting were not provided. As discussed previously, the prevalence of airway responsiveness may also lead to a decision to stop smoking. These limitations in study design must be considered in interpreting the associations among smoking cessation, nonspecific airway responsiveness, and annual decline in FEV_1.

Clinical Studies

Four small clinical studies have addressed airway responsiveness before and after smoking cessation. Buczko and coworkers (1984) studied 18 age- and sex-matched pairs of healthy nonatopic asymptomatic smokers and nonsmokers. Methacholine responsiveness was defined as the threshold dose causing a decrease in partial flows, measured at a volume of 40 percent of the VC above residual volumes (V_{40p}), below the 95-percent CI of CV. In the first part of the study, these researchers found that smokers had greater overall methacholine responsiveness than never smokers, but the difference was significant only for smokers with greater than 10 pack-years of cigarette consumption (Buczko et al. 1984). In the second part of the study, 17 smokers were studied with methacholine testing before and 3 months after smoking cessation. Threshold dose did not increase significantly for the group as a whole; however, airway responsiveness did decrease among a subset of five smokers with the greatest initial responsiveness.

Similar results were found by Simonsson and Rolf (1982) who measured methacholine responsiveness in 10 heavy smokers without symptoms or abnormal pulmonary function tests. They studied each subject 1 week before cessation and 1, 1.6, and 12 months after smoking cessation. Carboxyhemoglobin was measured to verify smoking abstinence. At baseline, only two subjects were responsive as determined by a 15-percent reduction in FEV_1 after inhalation of 0.1 percent methacholine. Within 1 month of abstinence, airways responsiveness decreased among four subjects. By 12 months, however, no further significant improvement in airway responsiveness was found for the group.

In contrast, Bolin, Dahms, and Slavin (1980) and Fennerty and coworkers (1987) found increases in airway responsiveness after cessation. Bolin, Dahms, and Slavin (1980) evaluated the effect of discontinuing smoking on methacholine sensitivity in seven asthmatic subjects. PC20 was measured before and 1 day after stopping smoking and was found to be 5.62 mg/mL and 1.56 mg/mL, respectively. This increase in airway responsiveness was seen among four of the seven subjects. Finally, Fennerty and colleagues (1987) recorded PD20 to histamine in 14 asthmatics before and 24 hours after smoking cessation. PD20 did not increase significantly. In seven subjects who abstained for 7 days, however, PD20 dose increased significantly (0.67 ± 0.43 mg/mL vs. 2.28 ± 2.03 mg/mL).

These studies are limited by short followup, small numbers of subjects, and a lack of adjustment for baseline airway caliber or pulmonary function. Additionally, the analyses did not control for seasonal variation in testing, and the latter three studies did not include a control group.

In summary, former smokers appear to have bronchial reactivity comparable with that of never smokers. The comparability of bronchial reactivity among former smokers and never smokers implies that smoking-induced changes in airway responsiveness may resolve with abstinence. Available data, however, are limited and not definitive. More research is needed to determine the interaction of smoking cessation with nonspecific airway responsiveness in altering rates of decline in ventilatory function.

PART IV. EFFECTS OF SMOKING CESSATION ON COPD MORTALITY

The Centers for Disease Control reported that 71,099 persons in the United States died in 1986 with COPD (ICD-9-CM 491-2, 496) as the underlying cause, and 164,049 persons died with COPD as the underlying cause or as a contributing cause (CDC 1989). It was estimated that 81.5 percent of COPD mortality was attributable to smoking (Table 11).

Data from both prospective and retrospective studies have consistently indicated an increased mortality from COPD in cigarette smokers compared with never smokers. In addition, the degree of tobacco exposure, as measured by the number of cigarettes smoked daily or duration of smoking, strongly affects the risk of death from COPD. This literature was reviewed in the 1984 Report of the Surgeon General (US DHHS 1984), in which cigarette smoking was identified as the major cause of COPD mortality for men and women in the United States. The proceedings of a recent workshop sponsored by NHLBI address the rise in mortality from COPD (Speizer et al. 1989).

Several prospective studies have shown that cessation of smoking leads to a decreased risk of mortality compared with that of continuing smokers (Table 12). In the British Physicians Study, Doll and Peto (1976) reported on a 20-year followup of 34,440 male British doctors who completed a questionnaire about their smoking behavior in 1951. Compared with never smokers, age-adjusted death rates for chronic bronchitis or emphysema were elevated for current smokers and for former smokers (mortality ratio=16.7 and 14.7, respectively).

TABLE 11.—Mortality attributable to COPD, United States, 1986

Smoking status	Crude prevalence (%)	Relative risk	Population attributable risk (%)	Estimated attributable deaths[a]
Current smokers				
Male	32.0	9.6	42.7	45,678
Female	24.0	10.5	54.3	31,049
Former smokers				
Male	34.9	8.7	41.7	44,604
Female	15.3	7.0	21.9	12,501
TOTAL			81.5	133,832

NOTE: COPD=chronic obstructive pulmonary disease.

[a]Includes deaths for which COPD was listed as either the underlying or a contributing cause of death.

SOURCE: CDC (1989).

A study of mortality among female British physicians has also been reported (Doll et al. 1980). A cohort of 6,194 female doctors who had responded to the 1951 questionnaire was studied for 22 years. The age-adjusted mortality ratio for chronic bronchitis and emphysema among continuing smokers increased with reported cigarettes smoked per day (Table 12). Former smokers had a mortality ratio of 5.0 compared with never smokers, which represented a reduction in mortality ratios of 52 percent (1 to 14 cigarettes/day) when compared with light smokers and of 84 percent when compared with heavy smokers (≥25 cigarettes/day).

Peto and coworkers (1983) reported COPD mortality based on a 20- to 25-year followup of 2,718 British men who had been enrolled in 5 different respiratory studies in the 1950s. There were no deaths attributed to COPD among never smokers. The ratio of observed to expected COPD deaths was 1.20 and 0.65 for current and former smokers, respectively, with expected deaths based on the entire cohort including smokers and nonsmokers. Thus, the mortality ratio for former smokers was 46 percent lower than that of continuing smokers (Peto et al. 1983).

Ebi-Kryston (1989) recently reported on chronic bronchitis mortality in a 15-year followup of 17,717 male British civil servants. Compared with never smokers, former smokers had a mortality ratio of 5.57 and continuing smokers had a ratio of 8.21. Thus, former smokers had a mortality ratio reduced by 32 percent compared with continuing smokers. Although the data were not presented for COPD, the author reported that the results were similar (Ebi-Kryston 1989).

In the United States, Rogot and Murray (1980) reported data on emphysema and bronchitis mortality among 293,958 U.S. veterans studied for 16 years. Former smokers were restricted to those who stopped smoking cigarettes for reasons other than a physician's orders. Current smokers had a mortality ratio of 12.07 compared with

TABLE 12.— Prospective studies of COPD mortality in relation to cigarette smoking status

Reference	Population	Followup	Cause of death		Standardized mortality ratio by smoking status		
					Never smokers	Former smokers	Current smokers
Doll and Peto (1976)	34,440 British male physicians	20 yr	Chronic bronchitis and emphysema		1.0	14.7	16.7
Doll et al. (1980)	6,194 British female physicians	22 yr	Chronic bronchitis and emphysema		1.0	5.0	1–14cig/day 10.5 15–24 cig/day 28.5 ≥25 cig/day 32.0
Rogot and Murray (1980)	293,958 US veterans aged 31–84	16 yr	Bronchitis and emphysema		1.0	5.2[a]	12.1
Peto et al. (1983)	2,718 British men (5 cohorts)	20–25 yr	COPD		0[b]	0.7[b]	1.2[b]
Carstensen, Pershagen, Eklund (1987)	25,129 Swedish men		Chronic bronchitis and emphysema		1.0	1.8	1–7 cig/day 1.9 8–15 cig/day 2.9 >15 cig/day 5.3
Ebi-Kryston (1989)	17,717 British male civil servants aged 40–64	15 yr	Chronic bronchitis		1.0	5.6	8.2
ACS CPS-II (unpublished tabulations)			COPD	Men Women	1.0 1.0	8.5 7.0	10.1 10.5

TABLE 12.—Continued

Reference	Population	Followup	Cause of death		Standardized mortality ratio by smoking status		
					Never smokers	Former smokers	Current smokers
Tockman and Comstock (1989)	17,036 Washington County, MD, men aged 35–85 at start of followup periods	13 yr	COPD	1963–68	1.00	2.5	2.5
				1969–75	0.0	1.5	3.6
	19,074 Washington County, MD, women aged 35-85 at start of followup periods	13 yr	COPD	1963–68	1.00	1.6	3.1
				1969–75	1.31	1.0	7.5
Marcus et al. (1989)	11,136 Japanese-American men in Hawaii, aged 45-65 at enrollment	20 yr	COPD	1965–69	1.00	7.0	3.9
				1970–74	1.4	4.3	1.8
				1975–79	2.0	1.9	2.7
				1980–84	1.7	1.1	5.7

NOTE: COPD=chronic obstructive pulmonary disease; ACS CPS-II=American Cancer Society Cancer Prevention Study II.

[a]Former smokers who stopped smoking cigarettes for reasons other than physician's orders.

[b]Observed deaths/expected deaths.

never smokers. Former smokers had a mortality ratio of 5.20 compared with never smokers.

The proceedings of the workshop sponsored by NHLBI on rising COPD mortality included several reports from population-based cohort studies (Speizer et al. 1989). Tockman and Comstock (1989) described mortality in more than 35,000 white residents of Washington County, MD, who were enrolled in 1963 and followed through 1975. Based on the 1963 smoking information, former smokers generally had lower mortality rates for COPD than did current smokers. Marcus and colleagues (1989) reported similar analyses for subjects in the Honolulu Heart Program cohort. Coding of death certificates for COPD differed substantially between the Honolulu Heart Program and the State Health Department. Mortality rates based on the Honolulu Heart Program coding showed a temporal pattern of declining mortality from COPD among former smokers with increasing mortality among the current smokers during the followup period 1965–1984.

Recent data from ACS CPS-II provide new evidence on mortality from COPD (ACS, unpublished tabulations). The age-adjusted death rates for COPD for men and women were approximately tenfold higher among current smokers compared with never smokers. The mortality ratios for male and female former smokers compared with never smokers were 8.5 and 7.0, lower than for current smokers (ACS, unpublished tabulations).

Several studies have reported on variation in COPD mortality by duration of abstinence (Table 13). In these studies, COPD mortality for former smokers initially increases after cessation above the rates for continuing smokers. The maximum mortality ratio for former smokers was found within the first 5 years of abstinence for ACS CPS-II and between 5 and 9 years after cessation for the British Physicians Study (Doll and Peto 1976). As discussed in Chapter 2, this initial increase in mortality probably reflects cessation by persons with smoking-related illnesses or symptoms. However, even in the U.S. Veterans Study (Rogot and Murray 1980), in which only former smokers who stopped for reasons other than a physician's orders were considered, death rates for emphysema and bronchitis among former smokers were higher than for those of current smokers after 5 to 9 years of abstinence.

Following this initial rise in COPD mortality after cessation, the mortality ratios drop with increasing duration of abstinence (Table 13). However, even after 20 years or more of abstinence, the risk of COPD mortality among former smokers remains elevated in comparison with never smokers.

PART V. FORMER SMOKERS WITH ESTABLISHED CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Effect of Smoking Cessation on FEV_1 Decline Among COPD Patients

The beneficial effects of smoking cessation on reducing the annual loss of pulmonary function are clearly shown in population studies and followup of smoking cessation participants. These populations have been relatively young and largely free of

TABLE 13.—Standardized mortality ratios for COPD among current and former smokers broken down by years of abstinence

Study	Current smokers[a]	Former smokers[a] by yr of abstinence					
		<1	1–2	3–5	6–10	11–15	≥16
ACS CPS-II (unpublished tabulations)							
Men <21cig/day	9.7	15.8	21.3	16.7	12.1	9.1	2.7
≥21 cig/day	13.5	22.6	28.5	25.9	20.2	12.6	4.5
Women <20 cig/day	6.1	11.5	10.0	12.6	3.5	3.4	2.6
≥20 cig/day	17.1	25.8	32.8	21.3	9.8	8.3	3.9
US Veterans Study (Rogot and Murray 1980)	Current smokers	Former smokers by yr of abstinence					
		<5	5–9	10–14	15–20	≥15	
	12.1	11.7	14.4	10.2	5.7	7.6	
British Physicians Study (men) (Doll and Peto 1976)	Current smokers	Former smokers by yr of abstinence					
		<5	5–9	10–14	≥15		
	35.6	34.2	47.7	7.3	8.1		

NOTE: COPD=chronic obstructive pulmonary disease; ACS CPS-II=American Cancer Society Cancer Prevention Study II.

[a]The reference category, never smokers, has a standardized mortality ratio of 1.0 by definition.

respiratory disease. The question arises whether the course of the disease can be influenced by smoking cessation once clinically overt COPD becomes apparent.

Hughes and coworkers (1982) examined the annual change in lung function among 56 male patients with radiologic evidence of emphysema. Patients who had stopped smoking prior to entry into the study and who did not smoke subsequently had a lower initial level of FEV_1 compared with patients who were smoking (45 vs. 55 percent predicted), but the annual rate of loss of FEV_1 for the former smokers was less (16.4±8.8 mL/year vs. 53.5±5.4 mL/year). Similar results were reported for annual decline of VC (14.9±18.6 mL/year vs. 53.1±11.3 mL/year). Diffusing capacity was lower at the initial assessment among smokers, 57 percent predicted, compared with former smokers, 75 percent, but diffusing capacity did not change significantly during followup.

Postma and coworkers (1986) examined the change in lung function in a 2- to 21-year followup of 81 patients with chronic airflow obstruction. Fifty-nine of the patients smoked throughout the study, and 22 stopped at the start or some time during followup. Initial level of FEV_1 was lower among former smokers, but the annual loss of FEV_1 was smaller (49±7 mL/year) than for smokers (85±5 mL/year).

In the National Institutes of Health Intermittent Positive Pressure Breathing Trial, 985 patients with COPD but without chronic hypoxemia were enrolled and studied for almost 3 years (Anthonisen et al. 1986). Spirometry was performed at entry and repeated every 3 months. The mean annual decline of FEV_1 was 44 mL per year; the investigators reported that neither past nor present smoking behavior affected the decline of FEV_1 although the data were not provided.

In summary, two of the three studies suggested that cessation of smoking is followed by a reduction of the annual loss of pulmonary function, even among patients with advanced COPD or emphysema. However, a beneficial effect of smoking cessation was not found in the large Intermittent Positive Pressure Breathing Trial. Additional investigation of the effect of continuing to smoke on lung function decline in patients with COPD is warranted.

Effect of Smoking Cessation on Mortality Among COPD Patients

The evidence for an effect of smoking cessation on survival of patients with COPD is limited. Traver, Cline, and Burrows (1979) found no association between the smoking status and the survival of 2 patient groups, 200 COPD patients in Chicago, IL, who were studied for 15 years and 100 patients in Tucson, AZ, evaluated for up to 7 years.

In a followup of up to 13 years, Kanner and coworkers (1983) examined the survival of 100 patients with chronic airflow limitation, aged 32 to 55 at enrollment. Twelve-year survival probabilities were 86, 79, and 64 percent for never, former, and current smokers, respectively.

Postma and colleagues (1985) studied survival of 129 patients with severe chronic airflow obstruction (FEV_1 ≤1,000 mL) for up to 18 years. All nonrespiratory deaths were censored. Patients were classified by the degree of reversibility of airflow obstruction. For both smokers and former smokers, relative survival was highest among those with the greatest reversibility of airflow obstruction. Smokers who quit smoking

before the start of followup had a higher survival rate than did continuing smokers (Figure 13). Within each stratum of reversibility, former smokers had lower mortality than current smokers.

In contrast, mortality in the 3-year followup period of the Intermittent Positive Pressure Breathing Trial was not significantly related to smoking status. The followup period was relatively brief, however. Patient age and the level of FEV_1 at enrollment were the strongest predictors of mortality.

In those prospective studies, smoking was evaluated on entry into the study. Subsequent changes in smoking status (i.e., smokers ceasing to smoke or former smokers reverting back to smoking) would reduce the estimated effects of smoking cessation compared with continued smoking. Overall, the extent of the evidence is limited, and a conclusion cannot yet be reached on the effect of smoking on mortality following diagnosis of COPD.

CONCLUSIONS

1. Smoking cessation reduces rates of respiratory symptoms such as cough, sputum production, and wheezing, and respiratory infections such as bronchitis and pneumonia, compared with continued smoking.

2. For persons without overt chronic obstructive pulmonary disease (COPD), smoking cessation improves pulmonary function about 5 percent within a few months after cessation.

3. Cigarette smoking accelerates the age-related decline in lung function that occurs among never smokers. With sustained abstinence from smoking, the rate of decline in pulmonary function among former smokers returns to that of never smokers.

4. With sustained abstinence, the COPD mortality rates among former smokers decline in comparison with continuing smokers.