were not introduced into Japan in large numbers until after the Second World War. The chronicity of tobacco use, particularly of those forms of tobacco that are commonly inhaled, is probably more important than age per se in producing COLD death. The chronicity of tobacco use differs in different countries and between men and women in the same country; these differences would be expected to result in different COLD mortality ratios.

In several of these prospective mortality studies, the mortality ratio for COLD deaths in smokers compared with nonsmokers was even larger than that found for lung cancer. This is consistent with the data in the previous chapter showing that cigarette smoking is the major predictor of decline in lung function and is also consistent with the clinical observation that clinically significant airflow obstruction is rare in the absence of a history of smoking.

### Retrospective Studies

The relationship between smoking and mortality from COLD was also examined in several large retrospective studies. Wicken (1966) conducted a study of 1,189 men living in Ireland who died from chronic bronchitis. Smoking habits were determined through personal interviews with relatives of the decedents. The relative risk for mortality from COLD was increased in smokers as compared with nonsmokers. Smokers of as few as 1 to 10 cigarettes per day had a 2.95-fold higher risk for mortality from COLD as compared with nonsmokers.

Dean and associates conducted two retrospective studies of the relationship between changes in smoking patterns and changes in mortality from bronchitis among a sample of the population in urban areas and in rural areas of northeast England. The periods of observation in the two studies were 1952 to 1962 (Wicken and Buck 1964; Wicken 1966) and 1963 to 1972 (Dean et al. 1977, 1978), respectively. Smoking status classifications in the two studies were similar, and were based upon questions relevant to the last 2 years before death or interview. In both studies, the relative risk for mortality from chronic bronchitis was substantially increased for smokers as compared with nonsmokers.

In summary, data from both the prospective and the retrospective studies consistently demonstrate an increase in mortality from COLD for smokers as compared with nonsmokers. These studies include populations of widely different ages, social and ethnic groups, geographic locations, and occupations; nevertheless, they strongly support a causal relationship between smoking and COLD.



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## TABLE 4.—COLD mortality rates for men and women, by number of cigarettes smoked per day, prospective studies

| Study | Men | | Women | | COLD disease classification |
|---|---|---|---|---|---|
| | Cigarettes per day | Mortality ratios | Cigarettes per day | Mortality ratios | |
| British physicians | Nonsmoker | 1.00 | Nonsmoker | 1.00 | Chronic bronchiti |
| | 1–14 | 17.00 | 1–14 | 10.50 | emphysema; or |
| | 15–24 | 26.00 | 15–24 | 28.50 | both |
| | 25+ | 38.00 | 25+ | 32.00 | |
| U.S. veterans | Nonsmoker | 1.00 | | | Chronic bronchiti |
| | 1–9 | 3.63 | | | |
| | 10–20 | 4.51 | | | |
| | 21–39 | 4.57 | | | |
| | 40+ | 8.31 | | | |
| | Nonsmoker | 1.00 | | | Emphysema |
| | 1–9 | 5.33 | | | |
| | 10–19 | 14.04 | | | |
| | 21–39 | 17.04 | | | |
| | 40+ | 25.34 | | | |
| | Nonsmoker | 1.00 | | | Chronic bronchiti |
| | 1–9 | 4.84 | | | and emphysema |
| | 10–19 | 11.23 | | | |
| | 21–39 | 17.45 | | | |
| | 40+ | 21.98 | | | |
| Canadian veterans | Nonsmoker | 1.00 | | | Chronic bronchitis |
| | 1–9 | 7.02 | | | |
| | 10–20 | 13.65 | | | |
| | 21+ | 14.63 | | | |
| | Nonsmoker | 1.00 | | | Emphysema |
| | 1–9 | 4.81 | | | |
| | 10–20 | 6.12 | | | |
| | 21+ | 6.93 | | | |
| Japanese | Nonsmoker | 1.00 | Nonsmoker | 1.00 | Emphysema |
| | <100,000[1] | 0.51 | <100,000 | 2.28 | |
| | <200,000 | 2.57 | <200,000 | 3.14 | |
| | >300,000 | 1.93 | >300,000 | 10.93 | |
| California men in various occupations | Nonsmoker[2] | 1.00 | | | Emphysema |
| | About ½ pk | 8.18 | | | |
| | About 1 pk | 11.80 | | | |
| | About 1½ pk | 20.86 | | | |
| American Cancer Society 9-State | Nonsmoker | 1.00 | | | All pulmonary diseases other than cancer[3] |
| | 1–9 | 1.67 | | | |
| | 10–20 | 3.00 | | | |
| | 20+ | 3.64 | | | |

[1] Data for the Japanese study are for lifetime exposure by > total number of cigarettes consumed.
[2] Nonsmoker in the California occupations study also includes > smokers of pipes and cigars.
[3] Pneumonia, influenza, TB, asthma, bronchitis, lung abscess, etc.

### Male and Female Differences in COLD Mortality

Mortality data presented by the National Center for Health Statistics indicate that in 1980 the number of deaths from COLD was 2.36 times higher among men than among women (9th ICDA nos. 490, 491, 492, and 494–496). In the prospective studies reviewed above, it is also apparent that the relative risk for death from COLD was greater for male smokers than for female smokers, although both male and female smokers exhibited a greater risk than nonsmokers for death from COLD. These differences are most likely a consequence of differences in male and female smoking patterns. The women in these studies tended to smoke fewer cigarettes, inhale less deeply, and begin smoking later in life than the men. They more frequently smoked filtered and low tar and nicotine cigarettes and had less occupational exposure to pulmonary irritants than men. These differences in mortality from COLD are narrowing because of a more rapid rise in female mortality from COLD (see Table 1).

Figures 6 and 7 help to explain the male–female differences in COLD mortality ratios in the prospective mortality studies and in U.S. COLD death rates. The figures are descriptions of the prevalence of cigarette smoking in successive 10-year birth cohorts of men and women as those cohorts progressed through the years 1900–1980 (Harris 1983). Examination of these figures revealed several important findings. Relatively few women took up smoking prior to 1930. The heaviest smoking cohorts of men have a prevalence of over 70 percent compared with 45 percent of women, and the male cohorts with these peak prevalences are older than the female cohorts. However, as discussed earlier, the incremental and progressive nature of cigarette-induced lung injury results in both prevalence and duration of cigarette smoking having an impact on COLD death rates. Therefore, in examining Figures 6 and 7 it is important to consider the span of years of a given prevalence of smoking maintained by a given birth cohort as well as the peak prevalence achieved by that cohort. The COLD death rates should then be proportional to the area under the prevalence curve described by each cohort, rather than to the peak of that curve.

A careful examination of Figure 6 reveals that the area under the prevalence curve for the cohort born between 1921 and 1930 is less than the area under the curve for the cohort born between 1911 and 1920, in spite of their similar peak prevalences. This difference is due to the more rapid decline in prevalence with age in the 1921 to 1930 cohort. Similarly, the cohort born between 1901 and 1910 partially compensates for a peak prevalence that is lower than the 1911 to 1920 cohort by having a somewhat a broader base. Each of the cohorts born prior to 1900 have substantially smaller areas under their curves than those born during the first three decades of this century. These differences in prevalence are reflected in the changes

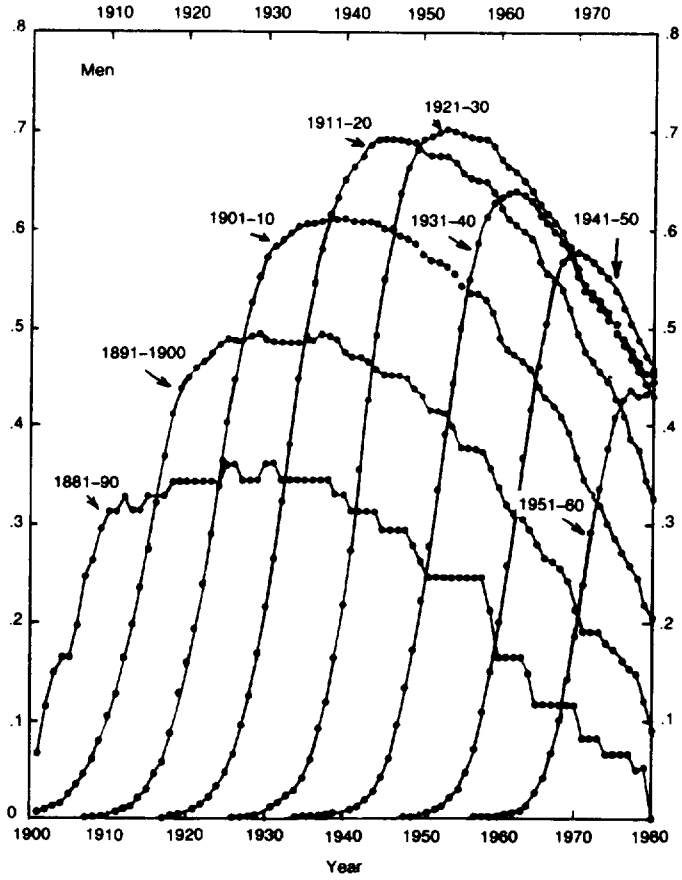


**FIGURE 6.—Prevalence of cigarette smoking among successive birth cohorts of men, 1900–1980, derived from smoking histories in the National Health Interview Survey (HIS)**

SOURCE: Harris 1983.

in age-specific death rates portrayed in Figure 8 and Table 5. The oldest age group (75–84) continues to show a rapid rise in COLD death rates as those birth cohorts with increasing prevalence and duration of smoking move into this age range. In the age range 65–74 the rates rose rapidly from 1960 through the mid 1970s, but seem to be leveling off, consistent with the fact that this age group is now made up entirely of men born after 1900. In the age range 55–64 the rates suggest a slight downturn beginning in the mid 1970s, coincident with the entry of the 1921 to 1930 birth cohort into this age group. The numbers for the age range 45–54 are too small to

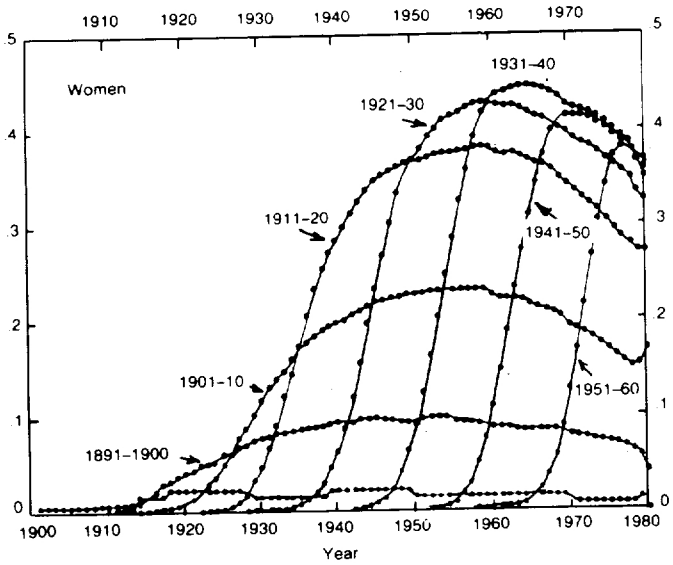


**FIGURE 7.—Prevalence of cigarette smoking among successive birth cohorts of women, 1900–1980, derived from smoking histories in the National Health Interview Survey (HIS)**

SOURCE: Harris 1983.

permit firm conclusions, but also suggest that a downturn in rates occurred in this group in the late 1960s.

A close examination of Figures 6 and 7 also offers an explanation of the differences in mortality ratios for men and women observed in the prospective studies. COLD is a slow, progressive disease, and death from COLD usually results only after extensive lung damage has occurred. The fact that death from COLD is unusual prior to age 45 reflects, in part, the 30 or more years required for cigarette smoke to damage enough lung to result in death. The substantial ventilatory reserve of the lung allows a significant amount of damage to exist in a person without symptomatic limitation or risk of death from COLD. The prospective mortality studies were conducted in the 1950s and 1960s, a point in time approximately 30 years after the beginning of the rise in smoking prevalence among women demonstrated in Figure 7. Even the older cohorts, where significant mortality might be expected, had begun smoking largely after 1930, and therefore had a shorter duration of smoke exposure than the men born in the same years. This shorter duration of the smoking habit, together with the previously described tendency of women to

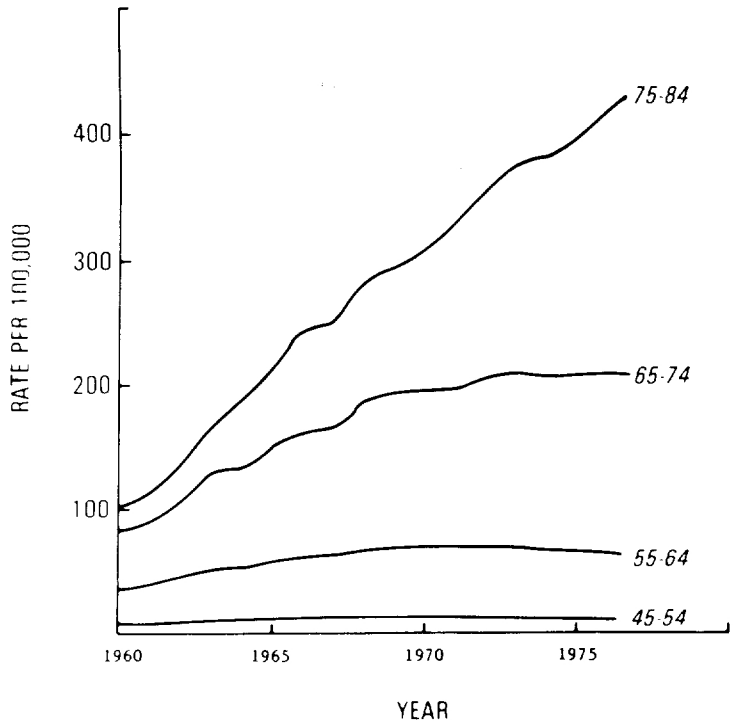


**FIGURE 8.—Age-specific COLD mortality rates for white men in the United States, 1960–1977**

NOTE: ICDA Nos. 490–492 and 519.3.
SOURCE: National Center for Health Statistics (1982).

smoke fewer cigarettes per day and to inhale less deeply, would be expected to result in less cumulative lung damage at any given age. This difference in extent of lung damage could explain the difference in COLD mortality ratios between men and women observed in the prospective mortality studies.

The British doctors study examined the risk of COLD death for male and female physicians who smoked similar numbers of cigarettes per day (Table 4), and the mortality ratios were similar for similar numbers of cigarettes smoked per day.

In summary, data from the prospective studies indicate that the relative risk of death from COLD is greater for male smokers than for female smokers. These differences are most likely a consequence of differences in female smoking patterns. Women tend to smoke fewer cigarettes, inhale less deeply, and begin to smoke later in life than men. These differences in mortality from COLD are narrowing because of a more rapid rise in female mortality from COLD than in male COLD mortality. This reflects the narrowing in differences between male and female smoking patterns and the rising prevalence of female smokers in successive cohorts born between 1920 and

**TABLE 5.—Age-specific COLD death rates per 100,000 population**

| Year | Age | | | |
|---|---|---|---|---|
| | 45–54 | 55–65 | 65–74 | 75–84 |
| 1960 | 8.6 | 36.1 | 82.9 | 101.8 |
| 1961 | 7.6 | 38.7 | 87.9 | 111.8 |
| 1962 | 9.6 | 44.2 | 107.2 | 136.7 |
| 1963 | 11.7 | 52.3 | 131.2 | 169.6 |
| 1964 | 12.1 | 51.8 | 131.6 | 181.9 |
| 1965 | 12.4 | 57.8 | 153.6 | 216.6 |
| 1966 | 12.4 | 61.9 | 161.9 | 244.8 |
| 1967 | 12.4 | 61.2 | 164.8 | 248.6 |
| 1968 | 13.1 | 67.4 | 186.7 | 286.5 |
| 1969 | 13.9 | 67.5 | 189.5 | 294.3 |
| 1970 | 13.6 | 68.1 | 196.5 | 311.5 |
| 1971 | 13.5 | 67.4 | 195.6 | 327.4 |
| 1972 | 13.0 | 67.7 | 204.8 | 351.4 |
| 1973 | 12.7 | 69.9 | 210.1 | 378.4 |
| 1974 | 12.8 | 64.8 | 204.8 | 380.4 |
| 1975 | 11.9 | 64.7 | 207.6 | 399.7 |
| 1976 | 12.2 | 64.0 | 210.7 | 419.7 |
| 1977 | 11.4 | 60.1 | 206.1 | 431.5 |

SOURCE: National Center for Health Statistics (1982).

1950. These data are ominous for women, portending a rising mortality from COLD over the next decades.

### Amount Smoked and Mortality From COLD

Six of the major prospective studies evaluated the influence of different smoking levels on mortality from COLD. These studies employed a variety of measures of tobacco exposure, including number of cigarettes smoked per day, grams of tobacco smoked, and total number of cigarettes smoked in a lifetime. The data, presented in Table 4, show a gradient in risk for mortality from COLD as the number of cigarettes smoked per day increases and as the cumulative number of lifetime cigarettes smoked increases. In the U.S. veterans study, smokers of two packs or more per day had 22 times the risk of COLD death of nonsmokers. Furthermore, mortality ratios between the two followup periods for bronchitis and emphysema actually increased overall and by the amount smoked (Figure 9). The authors noted that this was the only major disease of those associated with cigarette smoking that showed such an increase, suggesting that mortality ratios have been increasing over time at all levels of smoking. In the British and Japanese studies, women smokers at the highest levels exhibited a 32- and an 11-fold higher risk for death from COLD (respectively) than their nonsmoking counterparts. The variability in COLD mortality ratios noted in

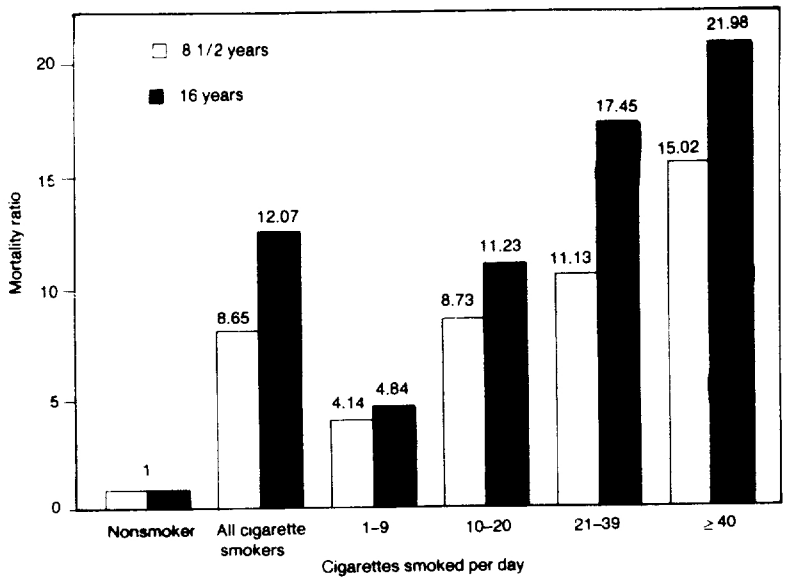


**FIGURE 9.—Bronchitis and emphysema for male smokers number of cigarettes smoked per day, U.S. veterans study, $8^1/_2$-year and 16-year followup**

Table 3 is much less evident when the mortality ratios are presented by amount smoked.

In summary, the degree of tobacco exposure strongly affects the risk for death from COLD in men and in women. This clearcut dose–response relationship enhances the strength of the causal relationship between smoking and COLD.

## Inhalational Practice and Mortality From COLD

The inhalation of tobacco smoke is the major mechanism whereby bronchial and alveolar tissues are exposed to the potentially damaging effects of tobacco smoke. In the British doctors study, subjects who acknowledged inhaling exhibited a 1.53-fold higher risk for COLD death as compared with those who stated they did not inhale (see Table 6). However, all smokers, regardless of their inhalational practice, exhibited higher risk for COLD mortality than did nonsmokers.

In the retrospective study from northeast England (Dean et al. 1977, 1978), the risk among men for mortality from chronic bronchitis steadily declined with a decrease in the depth of inhalation (Table 7). Among women, the risk for mortality from chronic bronchitis was lower for all other groups than for those who stated they "inhaled a lot."

**TABLE 6.—COLD mortality by inhalation practice, British doctors study, men**

| Cause of death | Number of deaths | Annualized death rate per 100,000 men responding to question: do you inhale? | | Risk in inhalers compared with unity in noninhalers |
|---|---|---|---|---|
| | | Yes | No | |
| Chronic bronchitis and emphysema and pulmonary heart disease | 71 | 89 | 58 | 1.53 |

**Table 7.—Relative risk for mortality by depth of inhalation, 1963–1972, second retrospective mortality study in northeast England**

| Depth of inhalation | Relative risk for chronic bronchitis | |
|---|---|---|
| | Men | Women |
| A lot (base) | 1.00 | 1.00 |
| A fair amount | 0.98 | 0.54 |
| A little | 0.62 | 0.41 |
| None | 0.58 | 0.58 |

SOURCE: Dean et al. (1977, 1978).

Results from prospective mortality studies comparing COLD death rates by inhalation are identical to those observed in the morbidity studies, which have consistently shown that COLD is more prevalent among inhalers than noninhalers (Ferris et al. 1972; Comstock et al. 1970; Rimington 1974).

These data suggest that inhalational practice affects the risk of mortality from COLD. People who inhale deeply experience a higher risk for mortality from COLD than people who do not inhale. Regardless of their inhalational practice, however, smokers still experience higher rates of death from COLD than nonsmokers.

## Age of Initiation and COLD Mortality

Another indicator of exposure to tobacco smoke that may influence risk for mortality from COLD is the age of initiation of smoking. If their smoking habits are otherwise similar, people who take up smoking at a younger age have a greater total exposure to tobacco smoke than those who take up smoking later in life, and might be expected to experience greater adverse consequences from smoking. In the Japanese prospective study (Hirayama 1981), men who began to smoke before the age of 19 exhibited slightly higher mortality ratios for emphysema than did men who began to smoke after the

**TABLE 8.—Number of deaths from chronic bronchitis, emphysema, and pulmonary heart disease in ex-cigarette smokers, by years of cessation, versus number of deaths in lifelong nonsmokers, British doctors study**

| | Number of deaths in ex-smokers, divided by number expected in lifelong smokers | | | | | Number of deaths in nonsmokers |
|---|---|---|---|---|---|---|
| Years of cessation | 0* | <5 | 5–9 | 10–14 | >14 | |
| | 35.6 | 34.2 | 47.7 | 7.3 | 8.1 | 2 |

* Current smokers.

age of 20. In the retrospective study from northeast England (Dean et al. 1977, 1978), the relative risk for death from chronic bronchitis among men who began to smoke after the age of 25 was 60 percent of that of men who began to smoke between the ages of 15 and 19. Among women in the same study who began to smoke between the ages of 15 and 19, the relative risk for death from chronic bronchitis was 1.28-fold higher than for women who began to smoke after age 25; however, the number of deaths was small.

### Smoking Cessation and COLD Mortality

The effects of smoking cessation on mortality from COLD were examined in the British doctors study and the U.S. veterans study. In the British doctors study, men who quit smoking experienced no change in mortality from COLD in the first 4 years and a rise in the next 5 years; presumably, this is related to the presence of many people in this group who quit smoking for health reasons (Table 8). Thereafter, ex-smokers experienced lower death rates from COLD, although their rates were still higher than those of the nonsmokers. Female ex-smokers also experienced lower mortality rates than current smokers, but the rates in ex-smokers were still higher than those in nonsmokers.

In the U.S. veterans study, ex-smokers who had quit for reasons other than ill health experienced lower mortality rates for COLD than did current smokers. However, the benefit of cessation upon risk for mortality was heavily dependent upon the prior level of smoking and the length of time of cessation. These data are presented in Table 9. Ex-smokers who had smoked less than 10 cigarettes per day had a 1.64-fold higher risk for mortality from COLD than nonsmokers; in contrast, ex-smokers who smoked more than 39 cigarettes per day had a 9.91-fold higher rate of death from COLD than nonsmokers. For any given number of cigarettes smoked

**TABLE 9.—Mortality ratios for bronchitis and emphysema in nonsmokers and in ex-smokers and current smokers by number of cigarettes smoked daily and number of years of cessation, U.S. veterans study**

| | Cigarettes/day | | | | |
|---|---|---|---|---|---|
| Smoking status | 0 | <10 | 10–20 | 21–39 | >39 |
| Nonsmoker | 1.00 | — | — | — | — |
| Ex-smoker | — | 1.64 | 5.35 | 7.68 | 9.91 |
| Current smoker | — | 4.84 | 11.23 | 17.45 | 21.98 |

| | | Years of cessation | | | | |
|---|---|---|---|---|---|---|
| Nonsmoker | Current smoker | <5 | 5–9 | 10–14 | 15–20 | >20 |
| 1.00 | 12.07 | 11.66 | 14.35 | 10.19 | 5.66 | 2.64 |

per day, however, ex-smokers had a lower risk than current smokers. As in the British study, mortality ratios initially increased over the first 9 years of cessation. After the first 9 years, mortality ratios for ex-smokers fell, but never reached the level of the nonsmoker.

Two studies have evaluated mortality rates from COLD among physicians, a group among whom many quit smoking to protect their health. Fletcher and Horn (1970) assessed the mortality rates from bronchitis among physicians in England and Wales. Among doctors aged 35 to 64, there was a 24 percent reduction in bronchitis mortality between 1953–1957 and 1961–1965, as compared with a reduction of only 4 percent in the national bronchitis mortality rates for men of the same age in England and Wales. Enstrom (1983) assessed mortality trends from COLD in a cohort of 10,130 physicians in California. The standardized mortality ratio for bronchitis, emphysema, and asthma among male California physicians relative to American white men declined from 62 during the period 1950 to 1959 to 35 during the period 1970 to 1979.

In summary, cessation of smoking leads to a decreased risk for mortality from COLD as compared with that of current smokers. The residual risk of death for the ex-smoker is determined by the person's prior smoking status and the number of years of cessation. However, the residual risk remains larger than that of the nonsmoker, presumably because of the presence of irreversible lung damage acquired during prior smoking.

## Pipe and Cigar Smoking Mortality From COLD

Several of the prospective epidemiological studies examined the relationship between pipe and cigar smoking and mortality from COLD. The data from these studies indicate that pipe smokers and

**TABLE 10.—COLD mortality ratios in male pipe and cigar smokers, prospective studies**

| Study | Category | Non-smoker | Type of smoking: Cigar only | Pipe only | Total pipe and cigar | Cigarette only | Mixed |
|---|---|---|---|---|---|---|---|
| American Cancer Society 9-State | COLD total | 1.00 | 1.29 | 1.77 | | 2.85 | |
| | Emphysema | | | | | | |
| | Bronchitis | | | | | | |
| British doctors | COLD total | 1.00 | | | 9.33 | 24.67 | 11.33 |
| | Emphysema | | | | | | |
| | Bronchitis | 1.00 | | | 4.00 | 7.00 | 6.67 |
| Canadian veterans | COLD total | | | | | | |
| | Emphysema | 1.00 | 3.33 | .75 | | 5.85 | |
| | Bronchitis | 1.00 | 3.57 | 2.11 | | 11.42 | |
| American Cancer Society 25-State | COLD total | | | | | | |
| | Emphysema | 1.00 | | | 1.37 | 6.55[1] | |
| | Bronchitis | | | | | | |
| U.S. veterans (8.5-year followup) | COLD total | 1.00 | .79 | 2.36 | .99 | 10.08 | |
| | Emphysema | 1.00 | 1.24 | 2.13 | 1.31 | 14.17 | |
| | Bronchitis | 1.00 | 1.17 | 1.28 | 1.17 | 4.49 | |
| U.S. veterans (16-year followup) | COLD total | 1.00 | 0.84[2] | 1.44[3] | | 4.75[4] | |
| | Bronchitis, emphysema | 1.00 | | 2.53[3] | | 13.13[4] | |

[1] Mortality ratios for ages 55 to 64 only are presented.
[2] Pure cigar.
[3] Pure pipe.
[4] Pure cigarette.

cigar smokers also experience higher mortality from COLD as compared with nonsmokers. However, the risk of dying from COLD is less than that of current cigarette smokers (Table 10).

## International Comparison of COLD Death Rates and Smoking Habits: The Emigrant Studies

Reid (1971) reported that age-adjusted mortality rates from chronic nonspecific lung disease among British citizens varied with migration patterns. British men living in the United Kingdom had a chronic, nonspecific lung disease death rate of 125 per 100,000, whereas migrants to the United States experienced a mortality rate of only 24 per 100,000, which is similar to the rate found in the U.S. population. Differences in cigarette smoking and air pollution were identified as the major factors contributing to the real excess in bronchitis morbidity experienced by the British in the United Kingdom. Rogot (1978) conducted a study of British and Norwegian emigrants to the United States. The mortality rate from chronic nonspecific lung disease (CNSLD) in Great Britain is about fivefold

that in the United States, whereas the mortality rate from CNSLD in Norway is slightly lower than that in the United States. In contrast, the British migrant rates were about equal to those of native-born Americans and the Norwegian migrant rates were the lowest. Mortality rates for CNSLD were higher for smokers than for nonsmokers in all groups. These data suggest that ethnic origin plays a minor role, if any, in determining COLD risk. Regardless of country of origin, these studies indicate that tobacco smokers experience higher mortality rates for COLD than do nonsmokers.

### COLD Mortality Among Populations With Low Smoking Rates

Numerous studies have reported that certain population groups who traditionally abstain from cigarette smoking for religious or other reasons have lower mortality rates from those diseases traditionally related to tobacco use. The 1982 and 1983 Reports of the Surgeon General, *The Health Consequences of Smoking* (USDHHS 1982, 1983), extensively reviewed this phenomenon as it relates to cancer and cardiovascular diseases among Mormons, Seventh Day Adventists, and others. Because Amish are seen as strict and fundamentalist in outlook, it is assumed that their use of tobacco is severely restricted. While cigarettes are largely considered taboo, pipe and cigar smoking and tobacco chewing are widespread (Hostetler 1968). Hamman et al. (1981) examined the major causes of death in Old Order Amish people in three settlements in Indiana, Ohio, and Pennsylvania to determine if their lifestyle altered their mortality risk compared with neighboring non-Amish. Mortality ratios from all respiratory diseases were significantly lower by over 80 percent in Amish men 40 to 69 years old, and by 50 percent in those 70 and older. In the chronic pulmonary disease categories including emphysema, bronchitis, and asthma, only one Amish male death occurred, whereas approximately 23 were expected. The pattern of mortality from chronic respiratory diseases was similar for Amish women.

### Summary and Conclusions

1. Data from both prospective and retrospective studies consistently demonstrate a uniform increase in mortality from COLD for cigarette smokers compared with nonsmokers. Cigarette smoking is the major cause of COLD mortality for both men and women in the United States.
2. The death rate from COLD is greater for men than for women, most likely reflecting the differences in lifetime smoking patterns, such as a smaller percentage of women smoking in

past decades, and their smoking fewer cigarettes, inhaling less deeply, and beginning to smoke later in life.

3. Differences in lifetime smoking behavior are less marked for younger age cohorts of smokers. The ratio of male to female mortality from COLD is decreasing because of a more rapid rise in mortality from COLD among women.
4. The dose of tobacco exposure as measured by number of cigarettes or duration of habit strongly affects the risk for death from COLD in both men and women. Similarly, people who inhale deeply experience an even higher risk for mortality from COLD than those who do not inhale.
5. Cessation of smoking eventually leads to a decreased risk of mortality from COLD compared with that of continuing smokers. The residual excess risk of death for the ex-smoker is directly proportional to the overall lifetime exposure to cigarette smoke and to the total number of years since one quit smoking. However, the risk of COLD mortality among former smokers does not decline to equal that of the never smoker even after 20 years of cessation.
6. Several prospective epidemiologic studies examined the relationship between pipe and cigar smoking and mortality from COLD. Pipe smokers and cigar smokers also experience higher mortality from COLD compared with nonsmokers; however, the risk is less than that for cigarette smokers.
7. There are substantial worldwide differences in mortality from COLD. Some of these differences are due to variations in terminology and in death certification in various countries. Emigrant studies suggest that ethnic background is not the major determinant for mortality risk due to COLD.

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# CHAPTER 4. PATHOLOGY OF LUNG DISEASE RELATED TO SMOKING

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## Introduction

It is usual to think of chronic airflow obstruction as being caused by airway narrowing or loss of airflow driving pressure—the elastic recoil of the lung (Macklem 1971)—or both. Lesions of the airways are often divided into those of the "large airways" and those of the "small airways." The reasons for this division are both historical and conceptual. Hogg et al. (1968) showed that in patients with chronic obstructive lung disease (COLD) the major site of airway obstruction lay in airways that were peripheral to the wedged catheter that the researchers used to partition airway resistance. The catheter was wedged in airways 2 or 3 mm in diameter, and thus the airways peripheral to the catheter included the smallest bronchi (airways with cartilage in their walls) and bronchioles (conducting airways without cartilage in their walls). Since both bronchi and bronchioles were involved, Hogg and associates used the term "small airways" to describe them, which has since become a popular term. Conceptually, lesions of airways may consist of an intraluminal component (mucus) or a mural component. Most of the mucus in the airways is thought to be secreted by the tracheobronchial submucosal glands (Reid 1960); these are mainly confined to airways more than 2 or 3 mm in diameter, or large airways. Because of the documented association between chronic productive cough and airflow obstruction (Fletcher et al. 1959), for a long time it was thought by many that intraluminal mucus was a major source of chronic airflow obstruction. Thus, the notion developed, without proper substantiation, that central airways obstruction was due to intraluminal mucus and peripheral airway obstruction was due to inflammation and narrowing. It is also true that many have equated emphysema with loss of elastic recoil, but when this has been examined in vivo (Park et al. 1970; Boushy et al. 1970; Gelb et al. 1973; Berend et al. 1979; Pare et al. 1982) or in excised lungs (Berend et al. 1980; Silvers et al. 1980), the association has not been close, with some notable exceptions (Niewoehner et al. 1975; Greaves and Colebatch 1980). Thurlbeck (1983) reviewed the evidence and argued that loss of recoil in emphysematous lungs may not be due to the lesions of emphysema per se but to defects in apparently morphologically normal intervening lung tissue.

The classical approach to considering the different sites of flow obstruction is used in this chapter to analyze the relationship between smoking and the morphologic lesions associated with chronic airflow obstruction in humans. Lesions of the large airways (bronchi) are discussed first, followed by small airways, and then by alveolated structures. It has very recently become apparent that it is important to include respiratory bronchiolitis as well as emphysema in the last category (Wright et al., in press); this issue is discussed in the paragraphs on peripheral (small) airways. Definitions and a brief

review of the diseases involved are provided. This chapter attempts to present the morphologic changes associated with chronic obstructive lung disease. The detailed epidemiologic and experimental evidence relating cigarette smoking and COLD are presented elsewhere in this Report.

## Lesions Associated With Chronic Airflow Obstruction

### Central Airways

*Mucus*

It is convenient to discuss intraluminal mucus and increased tracheobronchial mucus gland size together, because they are thought to be related (Reid 1960). Chronic bronchitis is defined as "the condition of subjects with chronic or recurrent excess mucus secretion into the bronchial tree" (Ciba Foundation Guest Symposium 1959). Because there is no way to accurately measure the amount of mucus secreted into the bronchi, the empirical approach was taken that production of any sputum was abnormal. Chronic was defined as "occurring on most days for at least 3 months of the year for at least 2 successive years" (Ciba Foundation Guest Symposium 1959). A further qualification was that such sputum production should not be on the basis of specific diseases such as tuberculosis, bronchiectasis, or lung cancer.

The initial step was to correlate chronic bronchitis, as defined above, with lesions in the central airways. This was first done by Reid (1960), who assessed gland size by comparing the thickness of the submucosal bronchial mucus glands in histologic sections to the thickness of the bronchial wall. The latter was defined as the distance from the basement membrane of the epithelium to the inner periochondrium. This measurement is now known as the Reid Index. This increase has been confirmed by several observers (Thurlbeck et al. 1963; Thurlbeck and Angus 1964; Mitchell et al. 1966; MacKenzie et al. 1969; Scott 1973), but not by all (Bath and Yates 1968; Karpick et al. 1970). An important observation was that there was a distinct overlap in the value of the Reid Index between bronchitics and nonbronchitics (Thurlbeck and Angus 1964) as opposed to Reid's 1960 finding that there were two completely separate groups. In practical terms, this meant that the Reid Index had limitations in predicting the presence or absence of chronic bronchitis. More important, it suggested a broad border between health (nonbronchitis) and disease (bronchitis). For a variety of technical reasons (Jamal et al., in press), the Reid Index is a difficult measurement to use; thus, other measurements of mucus gland size were developed. The most popular was the volume density of mucus glands, i.e., the ratio of area of mucus glands to area of the entire bronchial wall as seen on histologic slides (Hale et al. 1968; Dunnill

et al. 1969; Takizawa and Thurlbeck 1971; Oberholzer et al. 1978). Other methods included absolute gland size (Restrepo and Heard 1963; Bedrossian et al. 1971) and a radial intercept method (Alli 1975). The size of the acini (tubules) of mucus glands, the number per unit area, and the ratio of mucus to serous tubules have also been used (Reid 1960).

The Reid Index, the volume density of mucus glands, and the ratio of mucus to serous acini have been examined in smokers and nonsmokers; the results are shown in Table 1. When one considers the overwhelming association between smoking and chronic bronchitis in living subjects, differences in mucus gland size are insignificant. For example, three laboratories (Reid 1960; Thurlbeck et al. 1963; Thurlbeck and Angus 1964; Scott 1973) have found a difference in Reid Index between smokers and nonsmokers; two have not (Bath and Yates 1968; Hayes 1969). The results from volume density of mucus glands are clearer—Ryder et al. (1971) found a higher volume density of mucus glands in both male and female subjects. In populations of mixed sex, Cosio et al. (1980) and Pratt et al. (1980) found a higher volume density of glands, but Sobonya and Kleinerman (1972) and Scott (1973) did not. When observers have expressed their morphologic findings as either "normal" or "abnormal" (using different criteria), the smokers have been significantly abnormal in all the studies (Field et al. 1966; Megahed et al. 1967; Petty et al. 1967; Vargha 1969). The balance of the evidence is that there is an increase in mucus gland size in smokers. The discrepancy between the clinical and the morphologic findings may reflect several factors: the wide variation in mucus gland size in normal subjects, the difficulties in measuring the Reid Index and volume density of mucus glands, the different ways in which the cases have been collected, and the errors inherent in assessing smoking histories from analysis of charts; also, the fact that mucus glands can enlarge terminally (Helgason et al. 1970) might obscure true differences between the two groups. In addition, submucosal gland enlargement is a nonspecific change that can also occur in pneumoconiosis and cystic fibrosis.

Mucus is also secreted by goblet cells, most of which are in the major airways. Pratt et al. (1980) showed that goblet cells constituted 10.7 percent of the cells in the central airways of nonsmoking nontextile workers and 20.4 percent in smoking nontextile workers. Interestingly, they found an 18 percent frequency of goblet cells in nonsmoking textile workers; the frequency was about the same in smokers, whether or not they were textile workers.

### *Other Abnormalities of Central Airways*

A variety of other changes have been described in the central airways in patients with chronic airflow obstruction, including