lobe to measure lateral bronchial pressure and the other within the plethysmograph to record pleural surface pressure. MEFV curves were obtained in lungs ventilated with either air or a $HeO_2$ mixture. They found that an abnormal response to breathing $HeO_2$ is not necessarily indicative of either airway or parenchymal disease, and concluded that the ability of the $HeO_2$ breathing to discriminate between normal and obstructed peripheral airways is affected by large between-subject variation in normal maximal flow, which is probably due to normal variation in the caliber of the central airways. They therefore questioned the use of MEFV curves breathing air and $HeO_2$ as a means of distinguishing between peripheral and central airflow obstruction or as a means of identifying mild airflow obstruction due to structural changes in the small airways. A similar conclusion was reached by MacNee and coworkers (1983).

These structure–function correlation studies have provided fairly convincing evidence that at least some of the tests purported to measure small airways function can indeed identify structural changes in the small airways. These changes appear initially to involve macrophage accumulation around respiratory bronchioles, with subsequent development of epithelial abnormalities in the terminal bronchioles. With cumulative injury over a long period, chronic inflammation leads to fibrosis and perhaps to an increase in the amount of smooth muscle. These are strictly airway lesions. The alveolar wall destruction of emphysema is not as clearly related to the tests of small airways function (Petty et al. 1981).

### Acute Response to Cigarette Smoke

Before the tests of small airways function were introduced in the late sixties and early seventies, it was established that smoking a cigarette results in an immediate increase in airway resistance and a decrease in expiratory flow (Attinger et al. 1958; Chiang and Wang 1970; Clarke et al. 1970; Nadel and Comroe 1961; Robertson et al. 1969; Simonsson 1962; Zamel et al. 1963; Sterling 1967). It was thought that this response is mediated by the vagus nerve, and may be suppressed by isoproterenol and atropine (Nadel and Comroe 1961; Sterling 1967; Zamel et al. 1963).

Using the MEFV curve and closing volume, Da Silva and Hamosh (1973) showed a decrease in the maximum expiratory flow at 50 percent of the vital capacity, with the MEFV curve assuming a concave shape in 21 subjects immediately following cigarette smoking. Sobol et al. (1977) found the greatest change following smoking in airway resistance and specific conductance, with significant but lesser changes in the 1-second forced expiratory volume ($FEV_1$), the forced expiratory flow over the middle half of the forced vital capacity ($FEF_{25-75\%}$), and the ratio of $FEV_1$ to the forced vital capacity (FVC), $FEV_1$/FVC. Neither study found a change in closing volume.

From this limited information, it can be reasonably concluded that the large airways, rather than the small airways, respond acutely to the inhalation of cigarette smoke.

### Chronic Response to Cigarette Smoke

In the late 1800s, Mendelssohn (1897) reported that smoking had a deleterious effect on the respiratory system. The early studies were hampered by the lack of sensitive physiologic tests of lung function and relied heavily on differences between smokers and nonsmokers in the prevalence of respiratory symptoms. Confirmation of the structural basis of excessive respiratory symptoms seen in the smokers came from the classic paper by Reid in 1954, in which she described the pathology of chronic bronchitis (Reid 1954). Ventilatory limitation usually occurs late in the course of COLD. In contrast, the inflammatory response of the small airways is demonstrable relatively early in life in cigarette smokers.

#### *Smoking and Tests of Small Airways Function in Population Studies*

A large number of studies using tests of small airways function have been conducted over the past 15 years in groups and populations of various sizes, ages, and other characteristics. In some of these studies, the investigators have developed their own normal test ranges from a group of asymptomatic nonsmokers, but the normal ranges obtained by others (Buist and Ross 1973a, b; McCarthy et al. 1972; Collins et al. 1973) have been more commonly used.

In one of the earliest reported studies using the single breath $N_2$ test, Buist and coworkers (Buist and Ross 1973b; Buist et al. 1973) examined 1,073 persons attending a screening center, of whom 524 were current cigarette smokers. Among the smokers, an abnormal CV/VC was found in 35 percent, an abnormal CC/TLC in 44 percent, and an abnormal slope of the alveolar plateau in 47 percent. When the three measurements obtained from the single breath $N_2$ test were taken in conjunction, 64 percent of the smokers and 61 percent of the ex-smokers had an abnormal test result. In contrast, only 11 percent of the smokers had an abnormal $FEV_1$ and 21 percent had an abnormal $FEF_{25-75\%}$. This study suggested that the prevalence of measurable small airways dysfunction among cigarette smokers exceeds 50 percent. It must be kept in mind, however, that this study was carried out in a screening center and was therefore presumably biased toward a high disease prevalence.

A collaborative study was conducted in three North American cities (Montreal and Winnipeg, Canada, and Portland, Oregon)(Buist et al. 1979a) to avoid the pitfall of using a biased volunteer population. Random population samples were used in two of the cities and a random sample of a working population in the third. Only people aged 25 to 54 were studied. Among the nonsmokers in each of the three cities, the age-related regressions for the single breath $N_2$ variables (CV/VC, CC/TLC, and the slope of the alveolar plateau) and for $FEV_1/FVC$ had very similar slopes. As a result, a combined set of reference values was derived and used for comparison with the smokers and ex-smokers. No single test consistently showed the greatest prevalence of abnormality among the three cities. The slope of the alveolar plateau was abnormal most often in the women who smoked, and the CC/TLC was abnormal most often in the men who smoked. However, the prevalence of abnormalities was considerably lower than that reported in the screening center population study described above. Among the smokers for the three cities combined, CV/VC was abnormal in 17 percent of the men and in 26 percent of the women, CC/TLC was abnormal in 32 percent of the men and in 29 percent of the women, and the slope of the alveolar plateau was abnormal in 13 percent of the men and in 37 percent of the women. In comparison, the $FEV_1/FVC$ ratio was abnormal in 7 percent of the men who smoked and in 25 percent of the women who smoked.

In another large-scale study, Knudson and Lebowitz (1977) used the single breath $N_2$ test in a random, stratified, cluster sample of 1,900 white, non-Mexican-American residents of Tucson, Arizona. These investigators established their own reference values from the asymptomatic nonsmokers, and then compared their smokers to the reference values. Figure 2 reveals the prevalence of an abnormal test result in three groups: normals, asymptomatic smokers, and symptomatic subjects (a group comprised largely of smokers). For the $\dot{V}_{max\ 75\%}$ and slope of phase III as well as for combined parameters of the MEFV curve and single breath $N_2$ test, asymptomatic smokers had approximately twice the prevalence of abnormal test results compared with the normal nonsmoking population. When the analysis was limited to the population aged 25 to 54, the results were even more striking. Of the asymptomatic smokers, 21.5 percent had an abnormal $\dot{V}_{max\ 75\%}$, and 33.9 percent had some abnormality on either the single breath $N_2$ test or the MEFV curve.

Manfreda and coworkers (1978) studied population samples stratified by sex, age, and smoking habits from a rural community (Portage la Prairie) and an urban community (Charleswood) in Manitoba. They tested 246 persons in Portage la Prairie and 256 subjects in Charleswood. Reference values for asymptomatic nonsmokers were established for the single breath $N_2$ test variables and for $FEV_1/FVC$ and RV/TLC. In both communities, the slope of the alveolar plateau was abnormal (more than 2 SD from the mean) more often in smokers than in nonsmokers in both sexes (Figure 3).

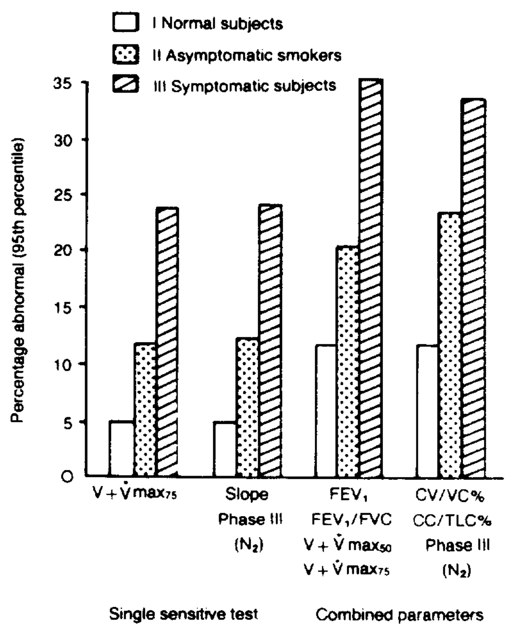


**FIGURE 2.—The relative sensitivity in three adult groups of a single sensitive test and of combined measurements for maximal expiratory flow volume (MEFV) versus closing volume (CV)**

NOTE: I = normal; II = asymptomatic smokers; III = symptomatic subjects.

SOURCE: Knudson and Lebowitz (1977).

Detels and coworkers (1979) studied population samples in two California communities, one being exposed to photochemical/oxidant pollutants (3,465 subjects). They used the single breath $N_2$ test, but measured the change in $N_2$ concentration between 750 and 1,250 $cm^3$ of expired air ($\Delta N_{2(750-1250)}$) rather than the more traditional way of looking at the slope of the alveolar plateau. They found that the mean values for $\Delta N_{2(750-1250)}$ and CV/VC were consistently higher for smokers than for nonsmokers.

Tockman and coworkers (1976) studied two groups of subjects selected from the Baltimore metropolitan area and not known to have disease. One group consisted of neighborhood control subjects participating in an epidemiologic study of obstructive pulmonary disease, and the other consisted of teachers in the Baltimore public schools who volunteered for a study of health and disease. Of the 133 subjects studied, 78 were smokers and 55 were nonsmokers. The investigators analyzed their data in a slightly different way from the approach used in the studies described above, in that they looked for differences between the age-related regression equations for the various tests in smokers and nonsmokers. They found significant differences between the adjusted mean smoker and nonsmoker

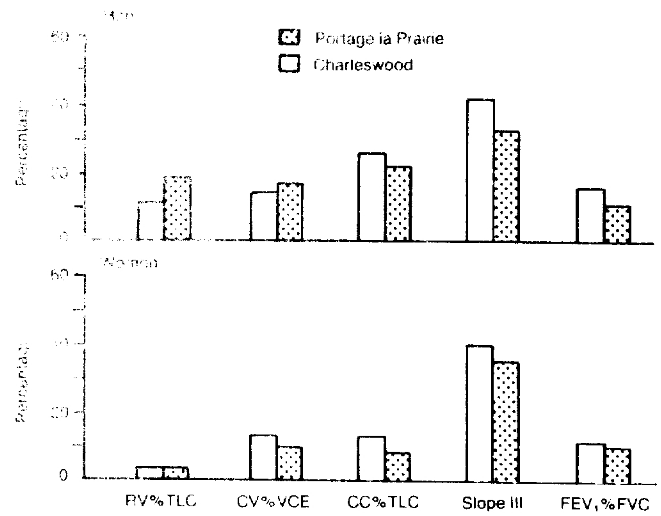


**FIGURE 3.—Prevalence of lung function abnormalities among smokers in an urban and a rural community**

SOURCE: Manfreda et al. (1978).

values, but no differences associated with age for CC/TLC, the slope of the alveolar plateau, RV/TLC, the steady state diffusing capacity, and the number of respiratory symptoms. Differences between smoker and nonsmoker mean values *and* an increasing difference between smokers and nonsmokers with increasing age were found for the $FEV_1$, $FEF_{25-75\%}$, $\dot{V}_{max\ 50}$, and moment analysis. The researchers suggest that the first group of tests may measure an all-or-none response that occurs relatively soon after the onset of smoking and is not affected by duration of smoking, and that the second group of tests may measure the effect of continued smoking, thus reflecting the increasing abnormality associated with longer exposure. This theory should be tested as part of an evaluation of the predictive value of small airways function.

Nemery and coworkers (1981) used the single breath $N_2$ test and MEFV curves to study a group of 272 European blue-collar workers, aged 45 to 55, from a steel plant near Brussels, Belgium. They first obtained reference values from their asymptomatic nonsmokers and defined their limit of normality as the 95th percentile for each of the tests. CC/TLC and the slope of the alveolar plateau had the highest prevalence of abnormality among the smokers (47 and 44 percent, respectively), followed by CV/VC% (34 percent), $\dot{V}_{max\ 75\%}$ (33 percent), and $\dot{V}_{max\ 50\%}$ (30 percent). When the indices derived from the single breath $N_2$ test were combined, 60 percent of their smokers had an abnormality in one or more of the measurements obtained from the test, whereas 52 percent had an abnormality in one or more measurements obtained from the forced expiratory maneuver. They pointed out that combining the measurements obtained from a test increases its sensitivity but decreases its specificity.

In addition to the studies described above, which involved fairly large population groups, numerous studies have been carried out in smaller groups (McCarthy et al. 1972; Stanescu et al 1973; Gelb and Zamel 1973; Cochrane et al. 1974; Abboud and Morton 1975; Marcq and Minette 1976). These studies have also found the measurements obtained from the single breath $N_2$ test and MEFV curve to be abnormal more often among smokers than among nonsmokers.

There have been very few published studies using MEFV curves with air and $HeO_2$ in reasonably large population groups. This is probably because the test is more difficult to perform than the single breath $N_2$ test or the forced expiration maneuver, and because of the wide range of within-individual and between-individual variability associated with these tests. Lam and coworkers (1981) obtained spirometry and MEFV curves with air and $HeO_2$ in 423 subjects participating in epidemiologic health surveys in British Columbia. The subjects consisted of four groups: nonsmokers and smokers not exposed to air pollutants at work, and nonsmoking and smoking grain elevator workers. Reference values were established from the 78 healthy, asymptomatic nonsmokers who were not exposed to any air pollutant at work. They found that in the subjects not exposed to air pollutants at work, $\dot{V}_{max\ 50}$ was the best test for discriminating the effects of cigarette smoking, but $\Delta\dot{V}_{max\ 50}$ and Viso$\dot{V}$ were not significantly different between the smokers and the nonsmokers. Interestingly, the $FEV_1$ was the best discriminator of the effect of grain dust, and there was poor concordance among the $FEV_1$, $\dot{V}_{max\ 50}$ and $\Delta\dot{V}_{max\ 50}$, and Viso$\dot{V}$. They concluded that a comparison of MEFV curves breathing air and $HeO_2$ is less helpful than the standard MEFV curves in distinguishing the effects of smoking and the effects of exposure to an air pollutant.

A careful evaluation of moment analysis in a reasonably large population group of adults has not been published. The limited information in the literature comes from studies of small groups of children (Neuberger et al. 1976; Liang et al. 1979; MacFie et al. 1979) and adults (Permutt and Menkes 1979; MacFie et al. 1979). These preliminary studies look promising, but a more extensive evaluation of the technique in carefully chosen population groups must be carried out before conclusions are reached on the value of this approach. Moment analysis is particularly sensitive to changes in the terminal part of the forced expiratory spirogram, which is particularly sensitive to an artifact in the MEFV curve when volume is measured by a spirometer at the mouth rather than by plethysmography. This artifact relates to the fact that there are volume changes due to gas compression that are measured by plethysmography but not by a spirometer at the mouth. The appropriate method to measure volume in moment analysis is by plethysmography, but very few such measurements have been made, most measurements having been made by spirometry. The magnitude of the resulting error has not been assessed.

In summary, the prevalence of abnormalities observed in any group of smokers depends on the age and characteristics of the group (how they were selected), on the reference values used (external reference values or reference values obtained from the population under study), and the cutoff used to define abnormality. However, this prevalence is uniformly higher in smoking than in nonsmoking populations. In a randomly selected sample of the general population below age 55, at least a third (and usually more) of the smokers can be classified as having small airways dysfunction.

*Dose–Response Relationship Between Amount Smoked and Small Airways Dysfunction*

In general, population-based studies involving adults of all ages with a reasonable range of cigarette consumption consistently show a fairly strong dose–response relationship between the number of cigarettes smoked and the degree of impairment.

Burrows and coworkers (1977a), studying a randomly stratified cluster sample of Tucson, Arizona, households comprised of 2,360 white, non-Mexican-American adults over age 14, found a highly significant quantitative relationship between pack-years of smoking and functional impairment, as measured by $\dot{V}_{max\ 75\%}$, $FEV_1$ percent predicted, and $FEV_1/FVC$ percent. The shift in the mean $FEV_1$ percent predicted and the distribution of the $FEV_1$ percent predicted with increasing cigarette consumption is illustrated in Figure 4.

Buist and coworkers found a positive correlation between total cigarette consumption and the frequency of abnormalities in tests of small airways function in 524 smokers attending an emphysema screening center. However, tests of significance were not reported in the description of the relationship between pack-years and CV/VC and CC/TLC (Buist et al. 1973). Tests of significance were reported in the description of the relationship between the slope of the alveolar plateau and cigarette consumption (Buist and Ross 1973b); no clear relationship between daily cigarette consumption and an abnormal slope of the alveolar plateau was found. Among women who smoked more than 20 cigarettes a day, however, the prevalence of an abnormal slope of the alveolar plateau was significantly increased;

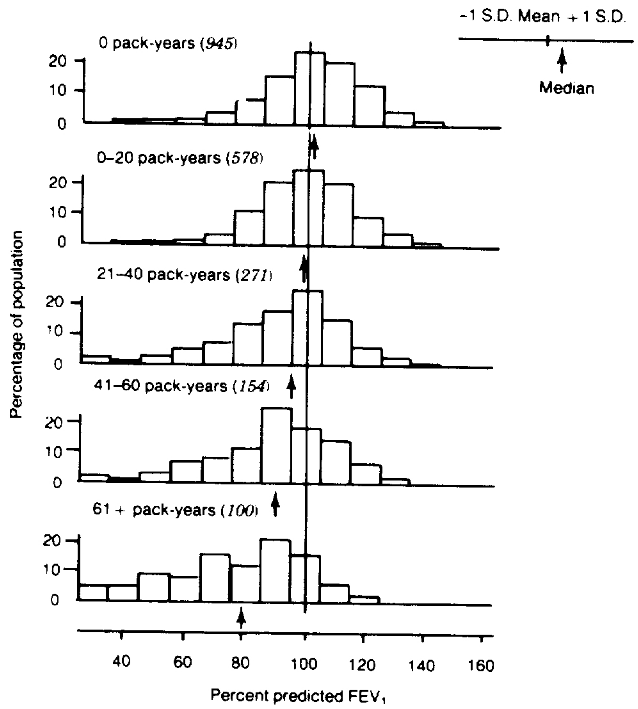


**FIGURE 4.—Percentage distribution of predicted forced expiratory volume in 1-second ($FEV_1$) values in subjects with varying pack-years of smoking**

* Subjects with "respiratory trouble" before age 16 are excluded.
NOTE: Means, medians, and ±1 standard deviation of the data for each group are shown in the abscissae.
SOURCE: Burrows et al. (1977a).

among men, a significant increase was found only for those who smoked more than 40 cigarettes a day.

Somewhat similar conclusions were reached by Tockman and coworkers (1976) in their study of healthy Baltimore residents. These investigators found that the CC/TLC, the slope of the alveolar plateau, RV/TLC, the steady state diffusing capacity, and respiratory symptoms were significantly different between smokers and nonsmokers, but there were no significant age-related differences for these variables. In contrast, tests of forced expiration ($FEV_1/FVC$, $\dot{V}_{max\ 50}$, and moment analysis) showed both differences between smokers and nonsmokers *and* increasing smoker versus nonsmoker differences with increasing age. These investigators interpreted their findings as suggesting that the tests of small airways function measure an all-or-none response that occurs at the onset of smoking but is not affected by duration of smoking. They proposed that the measurements obtained from a forced expiration maneuver probably measure the effects of continued smoking and reflect increasing abnormality associated with longer duration of smoking.

In their study of population samples in Manitoba, Manfreda and coworkers (1978) found a significant relationship between the current number of cigarettes smoked per day and the slope of the alveolar plateau and CC/TLC in both sexes and RV/TLC in women. These investigators found that an index of lifetime exposure to smoke had no effect after accounting for the effect of current smoking. Among all the lung function measurements, smoking status accounted for the largest proportion of variance due to the three smoking variables (smoker versus nonsmoker, number of cigarettes smoked per day, and lifetime amount smoked). They interpreted this finding as suggesting that responses on these lung function tests are related more to whether one does or does not smoke than to the amounts smoked.

Buist and coworkers, in the three-city collaborative study described earlier (Buist et al. 1979a), considered the effect of smoking in two ways, first by means of multiple regression analysis using age and cigarette-years data from both smokers and nonsmokers. Using the pooled data from the three cities, they found that cigarette consumption had a significant effect on the CC/TLC, CV/VC, the slope of the alveolar plateau, and $FEV_1/FVC$ (only in women). In this analysis, the effect of aging was considerably greater than the effect of smoking. The second approach involved data only from smokers, and a linear regression of the percentage of the predicted value for each variable on cigarette-years was obtained. A significant regression occurred in only one-third of the city/sex groups, and in each case the regression coefficients were very small. They concluded that a dose effect was not apparent when smokers only were considered, using both cigarettes per day and years smoked as indicators of cigarette consumption. They interpreted these findings similarly to Manfreda and coworkers (1978): it could be smoking itself and not the quantity of cigarettes smoked that is the crucial factor in the development of early functional impairment. The researchers suggest that absence of a clear-cut dose–response relationship in this study may also have resulted from the limited age range (25 to 54 years) and the relatively few heavy smokers in the study. They also speculate that the single breath $N_2$ test variables, especially the slope of the alveolar plateau, may be so "sensitive" that they reflect an on–off effect of smoking rather than cumulative damage.

Dosman and coworkers (1976) looked for a dose–response relationship in 49 smokers, aged 28 to 67, of whom 60 percent were attending a smoking cessation clinic. They found a significant relationship between a smoking index (cigarettes per day × years smoked) and $Viso\dot{V}$ and $\dot{V}_{max\ 50}$. They did not find a significant relationship between symptoms and frequency dependence of compliance, CC/TLC, the slope of the alveolar plateau, or $\dot{V}_{max\,50}$ (Figure 5).

Beck and coworkers (1981, 1982), in a cross-sectional study of three communities (Lebanon and Ansonia, Connecticut, and Winnsboro, South Carolina) sought a dose–response relationship in 1,209 smokers. Dividing the sample into light smokers (1 to 20 cigarettes/day) and heavy smokers (>20 cigarettes/day), they found a trend of increasing dysfunction across smoking categories that was evident as early as age group 15 to 24 for both men and women. A difference between men and women occurred in terms of the relationship between residual lung function (observed–predicted $FEV_1$) and pack-years of smoking. In male smokers, the combination of number of cigarettes smoked per day and duration of smoking was the best indicator of loss in lung function, as measured by residual lung function ($FEV_1$, $\dot{V}_{max\,50\%}$, and $\dot{V}_{75\%}$). For women smokers, pack-years best explained lung function loss as measured by residual lung function. These investigators thus found a very definite dose–response relationship between the amount smoked and lung function loss. They do point out, however, that smoking variables and age accounted only for up to 15 percent of the variation in residual lung function.

In summary, the data suggest a dose–response relationship between number of cigarettes smoked per day and the prevalence of abnormal results on tests of small airways function. That is, heavy smokers are more likely to have abnormal small airways function than light smokers. However, there is only a weak relationship between the degree of abnormality in small airways function and the number of cigarettes smoked per day or pack-years of smoking. In contrast, tests obtained from the forced expiration maneuver have a stronger dose–response relationship. This is consistent with the theory that cigarette smoking induces an inflammatory response in the small airways and that this response is more likely to happen in heavy smokers, as measured by sensitive measures of small airways function such as the single breath nitrogen test. The extent of chronic airway disease that reflects the dose and duration of the smoking habit is better measured by changes in the forced expiratory maneuver.

### *How Soon Do Changes in Small Airway Function Occur?*

The first study to look at the prevalence of abnormalities on tests of small airways function by age in a large group of smokers was reported by Buist and coworkers (1973a). These investigators found that abnormalities of small airways function could be detected before age 30 by means of the single breath $N_2$ test, with CV/VC discriminating best between smokers and nonsmokers in the age decade of the twenties (Figure 6).

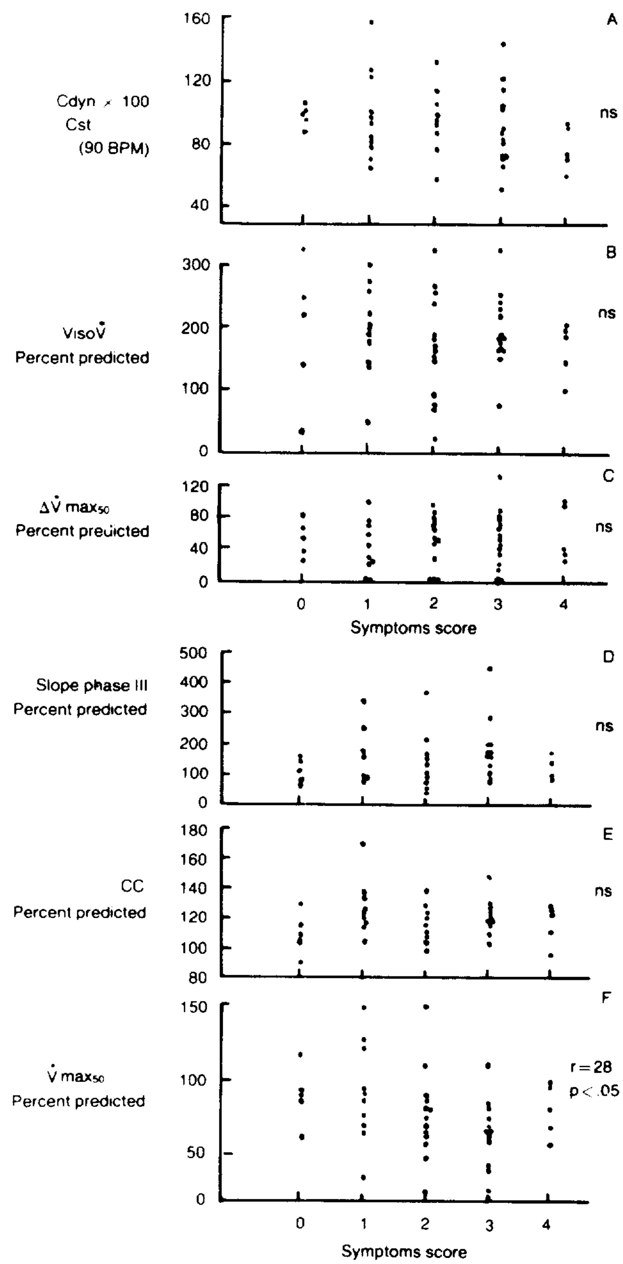


**FIGURE 5.—A composite of six tests plotted against symptoms score**

SOURCE: Dosman et al. (1976).

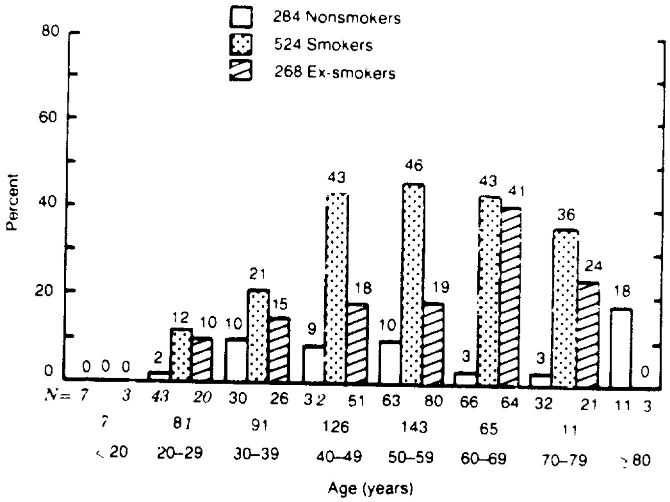


**FIGURE 6.—Prevalence of abnormal closing volume/vital capacity ratios in nonsmokers, smokers, and ex-smokers, by age decade**

SOURCE: Buist et al. (1973).

In their cross-sectional survey of residents in three separate communities in Connecticut and South Carolina, Beck and coworkers (1981, 1982) found that the age of onset of abnormalities in lung function may occur as early as age 15 to 24. Their approach used residual lung function (observed–predicted value) for $FEV_1$, $\dot{V}_{max\ 50\%}$, and $\dot{V}_{max\ 75\%}$, with a negative residual indicating an observed value below prediction. Negative residuals for all three measurements began to occur in women in the age group 15 to 24 (Figure 7). Significant differences among smoking categories—nonsmokers, ex-smokers, light smokers (1 to 20 cigarettes/day), and heavy smokers (>20 cigarettes/day)—were seen for $\dot{V}_{max\ 50\%}$ and $\dot{V}_{max\ 75\%}$ in women aged 15 to 24 and for $FEV_1$ in age group 25 to 34 (Figure 8). In male smokers, negative residuals began to occur for all three measurements in the age 25 to 34 group. Significant differences among the smoking categories were seen for $FEV_1$ in the 35 to 44 age group and for $\dot{V}_{max\ 50\%}$ and $\dot{V}_{max\ 75\%}$ in the 45 to 54 age group.

Seely and coworkers (1971) found lower values for $\dot{V}_{max\ 50\%}$ and $\dot{V}_{max\ 75\%}$ in a group of high school students with 1 to 5 years of smoking experience. These differences were significant in boys who smoked more than 15 cigarettes per day and in girls who smoked more than 10 cigarettes per day. Significant differences between the smokers and nonsmokers were not found for $FEV_1$.

Dosman and coworkers (1981) studied 1,202 adults, aged 25 to 59, living in Humboldt, Saskatchewan. Among smokers in the 25 to 29

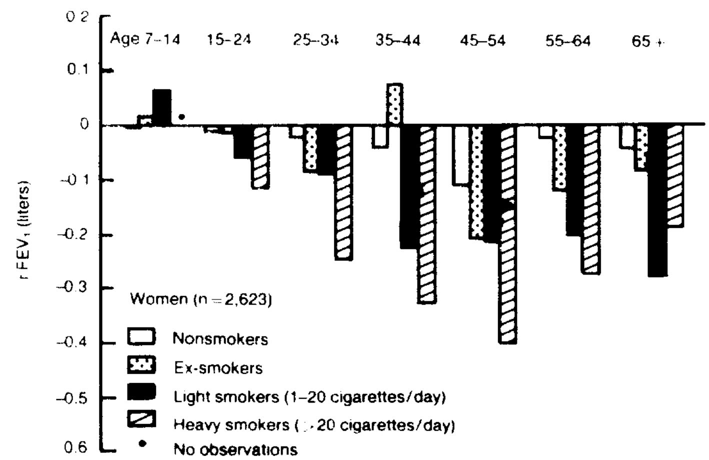


**FIGURE 7.—Mean residual FEV₁ in women, by smoking status and age**

SOURCE: Beck et al. (1981).

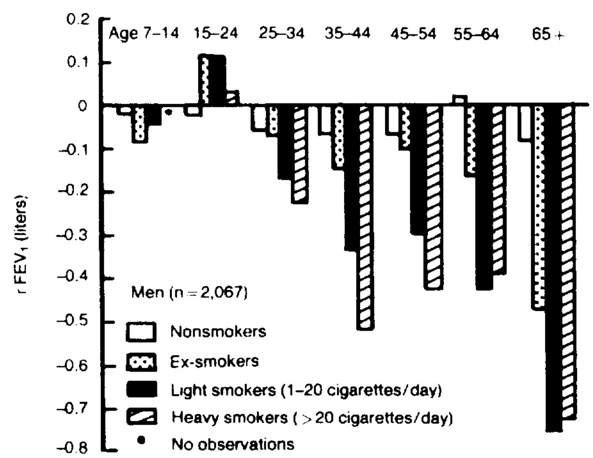


**FIGURE 8.—Mean residual FEV₁ in men, by smoking status and age**

SOURCE: Beck et al. (1981).

age group, 14.9 percent of the women and 18.5 percent of the men had an abnormal test value for the slope of the alveolar plateau, for CV/VC, or for both. Comparable rates of abnormality for $FEV_1/FVC$

were 2.1 percent in women and 5.6 percent in men. For both the slope of the alveolar plateau and CV/VC, the prevalence of abnormal test value increased steadily with increasing age, so that 63.6 percent of the female smokers aged 55 to 59 and 46.2 percent of the male smokers aged 55 to 59 had abnormal values. Comparable rates for an abnormal $FEV_1/FVC$ were 4.5 and 19.2 percent in the women and men, respectively.

Walter and coworkers (1979) studied 102 Indian male medical students in their late teens and early twenties. Of the 102 subjects, 60 were nonsmokers, 23 were light smokers (lifetime total of <10,000 cigarettes), and 19 were heavy smokers (lifetime total of >10,000 cigarettes). The researchers compared mean pulmonary function values obtained from the spirograms across the smoking categories. There was a consistent trend for all the lung function variables examined ($FEF_{20-30\%}$, $FEF_{35-55\%}$, $FEF_{70-80\%}$, $FEF_{80-90\%}$, $FEF_{25-75\%}$, and $FEV_1/FVC$), with the highest mean values being seen in the nonsmokers, intermediate values in the light smokers, and the lowest values in the heavy smokers. There were no significant differences among the three groups in height and weight. No information was given in this report about the type of cigarettes smoked.

The consistency of results from the studies attempting to define the age of onset of measurable abnormalities in tests of small airways function is striking. Even though statistical significance was not always found, the trend is clear and provides strong evidence that measurable abnormalities of small airways function do occur in some smokers within a few years of smoking onset.

### *Male-Female Differences in the Responses of the Small Airways to Cigarette Smoking*

When looking at variations between the sexes in response to cigarette smoking, one must take into account possible differences in the manner in which cigarettes are smoked, in the amount smoked, and in environmental exposures that may interact with smoking. Most investigators have found little or no difference based on sex for the relationship between the various tests of small airways function and age in nonsmokers. Thus, a difference between the sexes in response to smoking, if it exists, probably represents a true biological difference in the effect of smoking on lung function or variations in exposure dose resulting from method of smoking or amount smoked.

Unfortunately, the information available in the literature about sex-related differences in small airways response to cigarette smoking is scanty and conflicting. Manfreda and coworkers (1978) found a higher prevalence of abnormality in tests of small airways function among male smokers than among female smokers in their study of two communities in Manitoba. The opposite finding has been reported by Buist and coworkers (Buist and Ross 1973a, b; Buist et al. 1973, 1979a) in their studies of a screening center population and of population samples and groups in Montreal, Winnipeg, and Portland. It is quite possible that selection bias in the screening center study limits the ability to extrapolate this study to the general population. The three-cities study, however, did not suffer from that flaw, and showed clear differences (women higher than men) in the prevalence of abnormalities of CV/VC and the slope of the alveolar plateau. The prevalence of abnormality of CC/TLC, on the other hand, was slightly higher in male smokers than in female smokers (32 and 29 percent, respectively). A surprising finding was that the prevalence of $FEV_1$/FVC abnormality was considerably higher among women who smoked than among men who smoked (25 and 7 percent, respectively).

At this point, a generalization is not yet possible on sex-related differences in the response of the small airways to cigarette smoking. However, it seems likely that the contribution of sex difference is relatively small once age and dose are taken into account.

### Effect of Smoking Cessation on Small Airway Function

The correlation between abnormalities in tests of small airway function and the pathologic changes of inflammation of the small airways suggests that cessation of smoking may lead to a return toward normal in these tests. A number of authors have examined changes in tests of small airways function in cigarette smokers who have quit.

Ingram and O'Cain (1971) examined six smokers with an abnormal frequency dependence of compliance who quit smoking. After 1 to 8 weeks of cessation, values in all six returned to the normal range.

Bode et al. (1975) examined 10 subjects aged 29 to 61 with normal $FEV_1$ values while they were active smokers and again 6 to 14 months after they had stopped smoking. Static volume pressure curves, slope of phase III, and forced expiratory flow rates on air were unchanged by cessation. However, the maximum expiratory flow rates with helium at 50 and 25 percent of the vital capacity increased, and the volume of isoflow and closing volume decreased.

McCarthy et al. (1976) followed 131 smokers aged 17 to 66 who volunteered to attend a smoking cessation clinic. Cessation resulted in a significant reduction in the closing capacity (CC/TLC%) and the slope of phase III within 25 to 48 weeks in the 15 persons who were able to abstain from cigarettes completely.

Buist et al. (1976) followed a group of 25 cigarette smokers who attended a smoking cessation clinic and found that cessation resulted in significant improvements in the closing volume (CV/VC%), closing capacity (CC/TLC%), and the slope of the alveolar plateau (phase III) at 6 and 12 months following cessation.

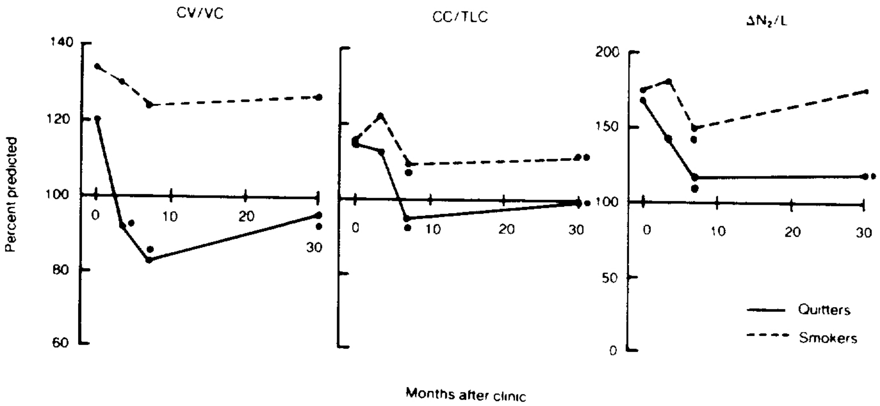


**FIGURE 9.—Mean values for the ratio of closing volume to vital capacity (CV/VC), of closing capacity to total lung capacity (CC/TLC), and slope of phase III of the single breath $N_2$ test ($\Delta N_2/L$), expressed as a percentage of predicted value (12, 13) in 15 quitters and 42 smokers, during 30 months after two smoking cessation clinics**

* A significant difference from the initial value at $p < 0.05$.

NOTE: Data from 3-month followup of the 1973 clinic and 4-month followup of the 1975 clinic have been combined, as have 6-month and 8-month data for the 1973 clinic.

SOURCE: Buist et al. (1979a).

This study was expanded using a second group of subjects (Buist et al. 1979b) and a 30-month followup. Once again, the three parameters of the single breath $N_2$ test showed improvement in smokers who quit; this improvement continued for 6 to 8 months, and then leveled off (Figure 9). In addition, the values for the single breath $N_2$ test in those who quit returned to the levels predicted for nonsmokers, suggesting that the changes in the small airways can be substantially reversed with cessation.

Bake et al. (1977) also showed an improvement in the slope of phase III following cessation in a small group who were followed for 5 months.

In summary, abnormalities in the small airways are substantially reversible in smokers who have not developed significant chronic airflow obstruction. This suggests that the inflammatory response in the small airways, which may be the earliest change induced by smoking, is also a change that reverses with the cessation of chronic exposure to the irritants in cigarette smoke.



480-144 O - 85 - 3

## Relationship Between Small Airways Disease and Chronic Airflow Obstruction

There is no question that the information obtained over the past 15 years from studies of small airways function has helped to describe more accurately the natural history of chronic airflow obstruction. The practical question of the place of tests of small airways function in clinical practice has not yet been resolved, and will not be fully answered until longitudinal studies using the tests have been completed. The important issue to be addressed is whether the tests of small airways function can be be used to identify the smoker who will progress to develop irreversible airflow obstruction. This question can be answered satisfactorily only by following a fairly large group of smokers prospectively over a period of time long enough for some of the smokers to develop an abnormal $FEV_1$. If the tests of small airways function can be used alone, or in conjunction with other qualitative or quantitative data about risk factors, they will clearly be useful to the practicing physician. If they are too sensitive or have a poor predictive value, their use will be more limited.

Buist and coworkers (1984) determined the positive and negative predictive value of tests of small airways function in their study of two cohorts followed prospectively over a 7- to 11-year period. They found that the positive and negative predictive values of the tests of small airways function varied greatly between the cohorts, largely because of the different ages and prevalences of an abnormal $FEV_1$ between the cohorts. They concluded that significant associations existed between the single breath $N_2$ test variables and spirometric variables in smokers, but the weakness of these associations and the high misclassification rates suggest that small airways disease does not necessarily lead to clinical airflow obstruction.

Over a period of 8 years, Marazzini and coworkers (Marazzini et al. 1977, 1981) followed a group of 69 asymptomatic workers in an iron foundry (49 smokers, 20 nonsmokers) living in the same area. They found that 39 percent of the smokers and 15 percent of the nonsmokers, initially diagnosed as having peripheral airways disease, developed central airways obstruction (defined as 1 or more of the vital capacity (VC), $FEV_1$ or $FEV_1/VC$ being more than 15 percent different from normal) within the 8-year followup.

An indirect way to assess the predictive value of the tests of small airways function was proposed by Tattersall and coworkers (1978). These investigators proposed that any valid test of chronic airflow obstruction must yield results that are systematically worse in middle-aged smokers than in middle-aged nonsmokers, and that such a test should also correlate with the $FEV_1$ in middle-aged smokers. Using these criteria in a cross-sectional study of a sample of working men in West London, they concluded that the most informative and repeatable tests were $\dot{V}_{max\ 75\%}$ and the slope of the alveolar plateau.

Nemery and coworkers (1981) addressed the question of the significance of tests of small airways function in their study of 2,072 blue-collar workers, aged 45 to 55, from a steel plant near Brussels. They found that smokers with an abnormal CC/TLC or slope of the alveolar plateau and a normal $FEV_1/FVC$ had a significantly lower $FEV_1/(height)^3$ than subjects with normal CC/TLC and slope of the alveolar plateau. They interpret their data as suggesting that smokers with small airways dysfunction experience a more rapid decline in $FEV_1$ than smokers without small airways dysfunction, leading to a higher susceptibility to long-term smoking effects in the former group.

The opposite conclusion was reached by Fletcher (1976), who examined the relationship between CV/VC, the slope of the alveolar plateau, and $FEV_1$ in 200 male smokers aged 40 to 55. In this group, he found a relatively poor correlation between $FEV_1$ and the single breath $N_2$ variables.

There is thus, as yet, inadequate information to allow a firm conclusion to be drawn about the predictive value of the tests of small airways function in identifying the susceptible smoker who is going to progress toward clinical airflow obstruction. The tests of small airways function are probably abnormal for many years before the $FEV_1$ becomes abnormal in those smokers who go on to develop airflow obstruction. However, many smokers with abnormal tests of small airways function may never develop clinically significant airflow obstruction. Therefore, functional changes in the small airways may not always be related to the widespread alveolar destruction seen in smokers or to the development of clinical airflow obstruction. It may be that varying degrees of inflammation and fibrosis occur in virtually all smokers, and that there is something very different about the smokers who develop extensive airway or emphysematous changes.

## Summary

A number of tests have been developed that can identify small airways dysfunction in individuals with normal lung volumes and standard measures of forced expiratory airflow. These tests correlate well with the presence of pathologic changes in the airways 2 mm or less in diameter, particularly with peribronchiolar inflammation. Cigarette smokers have a significantly higher frequency of abnormal tests of small airways function. Heavy smokers have a greater prevalence of small airways dysfunction than light smokers, but there is only a weak dose–response relationship between numbers of cigarettes smoked per day or duration of smoking and the extent of small airways dysfunction. This suggests that the response of the small airways may be an "all or nothing" inflammatory response to cigarette smoke irritants rather than a progressive response representing a cumulative injury.

Cessation of cigarette smoking results in significant improvement in small airways function, which in those smokers without evidence of chronic airflow obstruction, may return to normal.

The relationship between changes in the small airways and the development of chronic airflow obstruction remains unclear. It seems likely that those smokers who will go on to develop ventilatory limitation will have abnormal small airways function before the $FEV_1$ becomes abnormal, but many smokers with small airways dysfunction may never progress to significant airflow obstruction. Therefore, the usefulness of tests of small airways function for identifying those who will develop ventilatory limitation remains to be established.

## CHRONIC MUCUS HYPERSECRETION

### Introduction

The association of cigarette smoking and chronic cough was recognized by the general public in the term "smokers cough" well before the demonstration of this association in epidemiologic studies. Cough is the symptom most frequently experienced by smokers, and it is often accompanied by excess mucus secretion resulting in phlegm production or a "productive" cough. Chronic bronchitis was defined by the Ciba Foundation Guest Symposium report (1959) as "the condition of subjects with chronic or recurrent excess mucus secretion into the bronchial tree." The position was taken that any production of sputum was abnormal, and chronic was defined as "occurring on most days for at least 3 months of the year for at least 2 successive years." Also, the sputum production could not be on the basis of specific diseases such as tuberculosis, bronchiectasis, or lung cancer.

### Measurement of Cough and Phlegm in Epidemiologic Studies

The increasing use of standardized questionnaires in interviews to ascertain the presence of cough, phlegm, or other symptoms of respiratory disease has improved the quality of measurements of prevalence and incidence of these symptoms and the validity of comparisons within and between studies. Similar attention has been given to developing questions about smoking habits, including questions about the type and number of cigarettes used at the time of interview and in the past. The first British Medical Research Council (BMRC) questionnaire published in 1960 (Medical Research Council 1960) had been tested, revised, modified, and extended, and many studies have resulted from its widespread use. However, difficulties in using this questionnaire in epidemiological studies of populations in the United States and the desire to collect additional information led to modification in individual studies and to a loss of comparability between studies. This motivated the American Thoracic Society and the Division of Lung Diseases of the National Heart, Lung, and Blood Institute to establish the Epidemiology Standardization Project. Extensive methodological studies were done, standardized questionnaires were developed, and techniques for measuring pulmonary function and evaluating chest radiographs were proposed (Ferris 1978). Samet (1978) has reviewed the history of the development of respiratory symptom questionnaires. Although many investigators now use the methods advocated by the BMRC or the Epidemiology Standardization Project, several of the studies reviewed in this chapter of the Report are based on other, nonstandard questionnaires. A comparison between studies of different populations, or the same population studied at different times, must be made cautiously and only after careful consideration of technical and methodological issues. Low rates of participation and use of unrepresentative samples may cause biased estimates of the frequency and distribution of symptoms. Attitudes toward smoking have changed, and comparisons of questionnaire responses and objective measurements of smoking habits indicate that at least in some situations, less reliance can now be placed on answers to questions about smoking habits (MRFIT Research Group 1982). Estimates of prevalence and incidence of respiratory symptoms are imprecise, and too much importance should not be attached to relatively small differences in rates of reporting cough and phlegm. Each author's criteria for detecting the presence of cough or phlegm should be considered, especially when combinations of symptoms or diagnostic labels such as chronic bronchitis or mucus hypersecretion are used. Notwithstanding methodological differences, however, consistent patterns or trends found in many studies indicate that the associations between smoking and chronic mucus hypersecretion are real and that the findings are widely applicable.

### Prevalence of Cough and Phlegm

Unpublished data from the National Center for Health Statistics estimate that there were almost 8 million persons with chronic bronchitis in the United States in 1981 (3.4 million men, 4.5 million women). This is probably an underestimate of the true frequency of cough and phlegm in the population, since people who had these symptoms were not counted as chronic bronchitics unless they responded affirmatively to the question about bronchitis. On the other hand, some cases of acute bronchitis may have been included incorrectly and inflated the estimate. The apparently higher prevalence rates of chronic bronchitis in women than in men in the National Health Interview Surveys in 1970 and 1979 (3.4 and 3.7 percent for women in 1970 and 1979, respectively, and 3.1 and 3.2 percent for men in 1970 and 1979) are probably due to ascertainment being less complete for men (USDHEW 1980b). Prevalence rates of chronic bronchitis ranged from 4.2 percent at ages under 17 years to 2.7 percent at 17 to 44 years, 3.6 percent at 45 to 64, and 4.5 percent at ages over 65 years. The high rate in the youngest group is presumably because of the inclusion of cases of acute bronchitis.

Standard questions about chronic cough were asked in the National Health and Nutrition Examination Surveys (NHANES) of representative samples of the U.S. population. Some supplementary questions were asked about phlegm and other respiratory symptoms, and these data are presented in the appendix to this chapter. Prevalence rates of diagnosed chronic cough in 18- to 74-year-old participants in NHANES 1 (1971–1975) were 3 percent for men and 2

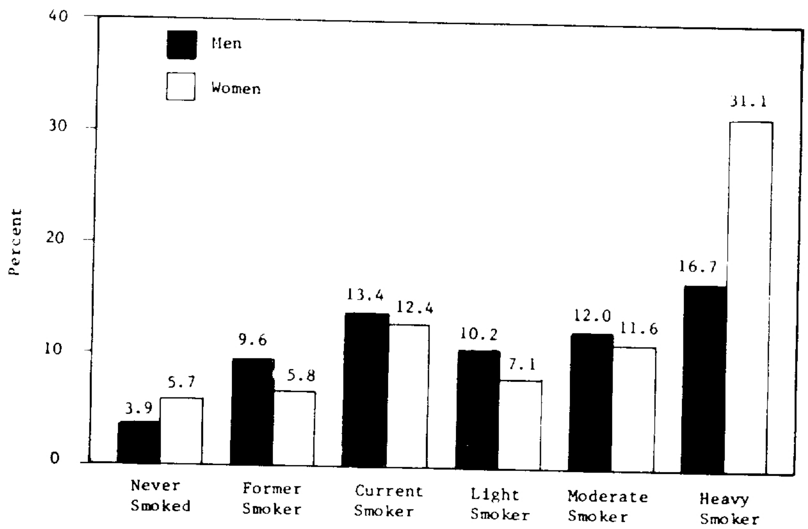


**FIGURE 10.—Percentage of recurring persistent cough attacks by sex and smoking status for adults 25–74, United States, 1971–1975**

NOTE: Light smoker: 1–14 cigarettes per day
Moderate smoker: 15–24 cigarettes per day
Heavy smoker: ≥ 25 cigarettes per day

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

percent for women; they increased with age from 1 percent at 18 to 24 years to 6 percent at 65 to 74 years for men, and from 1 percent at 18 to 24 years to 3 percent at 65 to 74 years for women (National Center for Health Statistics, unpublished data).

The prevalence of self-reported recurring persistent cough by smoking status for men and women of different ages is presented in the appendix and in Figure 10 based on NHANES 1. For the entire NHANES population, the prevalence of the persistent cough increased threefold in male smokers and twofold in female smokers compared with nonsmokers (Figure 10), and the prevalence of cough increased with increasing cigarette consumption in both men and women.

## Relationship of Cough and Phlegm to Smoking

Relationships between smoking and cough or phlegm are strong and consistent; they have been amply documented and are judged to be causal (USPHS 1964, 1971; USDHEW 1979; USDHHS 1980a, 1981). Associations between smoking and cough or sputum are apparent in the recent studies listed in Tables 2 and 3 and are illustrated in Figures 11 and 12. Although cough, phlegm, and chronic bronchitis occur in nonsmokers, prevalence rates are consistently higher in cigarette smokers.

The excess prevalence of cough and phlegm in cigarette smokers increases with the amount smoked (see below). The frequency of reporting cough and phlegm is at least twice as high for smokers as for nonsmokers except in some groups with minimal exposure. Differences in prevalence rates between smokers and nonsmokers tend to be greater at older ages among men, whereas differences in rates between smoking and nonsmoking women tend to be as great or greater at younger ages (Tables 2 and 3). Rates are not given for pipe or cigar smokers in most of these studies, presumably because the numbers of such smokers were too small for reliable rates; male pipe smokers and cigar smokers in Tecumseh reported cough and phlegm more frequently than nonsmokers or ex-smokers, but less frequently than cigarette smokers (Higgins et al. 1977).

Individual studies have evaluated other factors as well as smoking, but smoking has been judged the most important determinant of symptom prevalence (Fletcher et al. 1976; Ferris et al. 1976; Kiernan et al. 1976; Bouhuys 1977; Higgins et al. 1977). Consideration of evidence from many different studies has led to the conclusion that cigarette smoking is the overwhelmingly most important cause of cough, sputum, chronic bronchitis, and mucus hypersecretion (Speizer and Tager 1979; USDHHS 1980b).

*Effects of Smoking Cessation*

Cross-sectional information on ex-smokers suggests that stopping smoking is followed by a reduction in cough and phlegm because symptoms are less prevalent than in current smokers, but these symptoms are generally more prevalent in ex-smokers than in lifelong nonsmokers (Huhti et al. 1978; Gulsvik 1979; Park 1981; Schenker et al. 1982). However, the differences between ex-smokers and nonsmokers were either very small or absent in the studies reported by Higgins et al. (1977) and Manfreda et al. (1978).

The longitudinal studies cited in Table 3 strengthen the evidence from cross-sectional studies that cigarette smoking causes cough and phlegm. Prevalence rates were higher at followup examinations in persons who started to smoke after being nonsmokers at a previous examination (Kiernan et al. 1976; Leeder et al. 1977). Rates of reporting cough or phlegm decreased in smokers who stopped smoking in two British studies (Kiernan et al. 1976; Leeder et al. 1977) and in populations in the United States (Ferris et al. 1976; Friedman et al. 1980; Beck et al. 1982). Many people who stop smoking report a rapid reduction in cough and phlegm. Although remission of symptoms occurs in some persistent smokers, remission rates are generally higher and incidence rates lower in those who quit than in those who continue to smoke.

**TABLE 2.—Prevalence (percent) of cough, phlegm, and other symptoms for nonsmokers (NS), smokers (SM), and ex-smokers (EX), cross-sectional studies**

| Author, year, country | Population | Cough | Phlegm | Other | Comments |
|---|---|---|---|---|---|
| Tager and Speizer, 1976, U.S. | 507 residents, aged 15–65+, East Boston | Chronic bronchitis | | | Chronic bronchitis (cough and phlegm ≥3 mos/yr for 2 years); no age trend for either sex after adjusting for smoking; prevalence greater for men than women at each age; significant increase in chronic bronchitis with increased lifetime cigarette consumption for current smokers, but not ex-smokers |
| | | Men | | | |
| | | NS | 7.0 | | |
| | | SM (pack-years) | | | |
| | | 1–5 | 8.7 | | |
| | | 5–10 | 25.0 | | |
| | | 10–20 | 28.6 | | |
| | | >20 | 47.5 | | |
| | | Women | | | |
| | | NS | 4.6 | | |
| | | SM (pack-years) | | | |
| | | 1–5 | 14.3 | | |
| | | 5–10 | 9.1 | | |
| | | 10–20 | 20.8 | | |
| | | >20 | 30.0 | | |

## TABLE 2.—Continued

| Author, year, country | Population | Cough | | Phlegm | | Other | | Comments |
|---|---|---|---|---|---|---|---|---|
| Dean et al., 1978 United Kingdom | 6,277 men and 6,459 women, aged 37–67, England, Scotland, and Wales | Morning cough | | | | Bronchitis syndrome | | Bronchitis syndrome (cough and phlegm 3 mos/yr, shortness of breath); significant increase of all symptoms with age; prevalence of cough, phlegm, and wheeze increased with number of cigarettes smoked; filter vs. nonfilter cigarette effects small, nonsignificant for most symptoms |
| | | | | Men | | | | |
| | | NS | 12.5 | NS | 11.4 | NS | 3.5 | |
| | | SM (filter) | | SM (filter) | | SM (filter) | | |
| | | 1–7 | 19.6 | | 14.4 | | 5.1 | |
| | | 8–12 | 32.8 | | 20.8 | | 8.6 | |
| | | 13–17 | 36.3 | | 25.4 | | 9.4 | |
| | | 18–22 | 44.0 | | 26.9 | | 8.5 | |
| | | 23–27 | 50.6 | | 34.2 | | 1.0 | |
| | | 28–32 | 56.8 | | 34.5 | | 8.7 | |
| | | 33+ | 52.1 | | 28.4 | | 13.8 | |
| | | | | Women | | | | |
| | | NS | 9.8 | NS | 7.5 | NS | 2.5 | |
| | | SM (filter) | | SM (filter) | | SM (filter) | | |
| | | 1–7 | 16.9 | | 13.8 | | 3.8 | |
| | | 8–12 | 25.8 | | 16.6 | | 4.2 | |
| | | 13–17 | 29.6 | | 16.6 | | 5.1 | |
| | | 18–22 | 45.1 | | 25.8 | | 10.6 | |
| | | 23+ | 56.6 | | 34.3 | | 12.0 | |