

“The term asthma is not appropriate for the bronchial narrowing which results solely from widespread bronchial infection, e.g., acute or chronic bronchitis; from destructive diseases of the lung, e.g., pulmonary emphysema; or from cardiovascular disorders. Asthma, as here defined, may occur in vascular diseases, but in these instances the airway obstruction is not causally related to these diseases.”

In rare instances, allergy to tobacco products has been ascribed a causative role in asthma (99, 105, 168, 169, 189). Support for this association comes largely from the presence of skin test reactions to tobacco products and passive transfer tests (168, 169).

In the “Tokyo-Yokohama Asthma” studies, a severe asthma-like disease, presumed to be caused by air pollution, affected cigarette smokers predominantly (155). The absence of smoking data on unaffected members of the same population leaves the question of an additive effect of cigarette smoking unanswered. One study suggests that non-smokers may have a slightly greater prevalence of asthma than smokers; the possibility of bias due to self-selection of the base population could not, however, be excluded in this study (84).

Apart from the exceptions noted above, it is clear that cigarette smoking is of no importance as a cause of asthma. A hypothetical contraindication to cigarette smoking can be postulated for asthmatics on the basis of the physiologic alterations induced in the tracheobronchial tree by tobacco smoke. Nonetheless, substantiation of worsening from cigarette smoking in asthmatics has not been reported frequently. A cause-and-effect relationship between cigarette smoking and asthma, as defined above, is not supported by evidence available.

RELATION OF SMOKING AND INFECTIOUS DISEASES

The category, influenza and pneumonia (ISC 480-493), contributed to the excess mortality of smokers observed in six of seven prospective studies (Chapter 8, Tables 19 and 26). Details sufficient to warrant conclusions about the nature of this association are not presented in these studies, nor has the apparent association been evaluated further by careful epidemiological research.

Studies adequate for examination of this association are available for only two categories of infectious diseases, upper respiratory viral illness and tuberculosis (30). Experiments on transmission of common colds failed to demonstrate increased susceptibility in volunteers with a history of cigarette smoking (50). Moreover, common colds were detected among 5,500 employees over a 2-year period with approximately the same frequency in smokers and non-smokers (110). In a study of illness in a group of families under close observation for several years, the frequency and severity of common respiratory diseases, such as the common cold, rhinitis, laryngitis, acute bronchitis, and nonbacterial pharyngitis, were the same in cigarette smokers and non-smokers (21). Similar results were obtained by questionnaires in an analysis of the frequency of common colds in a group of college graduates followed over a 20-year period (85).

A number of studies have suggested a substantial relationship between smoking and pulmonary tuberculosis (55, 124, 133, 175). The possibility that the relationship is not a direct one needs further careful examination. Certain social factors, important to epidemiological assessment in tuberculosis, have not been considered in detail in these studies. Of particular interest in this regard is a study (29) in which both cigarette and alcohol consumption were found to be in excess in tuberculosis patients as compared to the matched controls. The number of cigarettes consumed in the two groups was the same, however, at each level of alcohol intake. Matching by cigarette consumption failed to weaken the association between alcohol consumption and tuberculosis (29). Thus, the relationship between tuberculosis and smoking in this study was only an indirect one; the association was found to occur between smoking and alcohol consumption and between alcohol consumption and tuberculosis, rather than between smoking and tuberculosis.

Thus the association between smoking and the infectious diseases is confined at present to a single cause-of-death category: Influenza and pneumonia contribute to the excess deaths in cigarette smokers, but the data are insufficient to evaluate this observation. In the limited number of studies available, cigarette smoking has not been shown to contribute to the incidence or severity of either naturally acquired or experimentally induced upper respiratory viral infections.

CHRONIC BRONCHOPULMONARY DISEASES

Mortality for certain respiratory diseases (bronchitis, bronchiectasis, chronic pulmonary fibrosis, chronic interstitial pneumonia, and emphysema) increased in the decade 1949-1959 (48) and continues to show an upward trend (132, 141). In 1955, cancer of the lung was certified as the underlying cause of death in 27,133 persons and chronic bronchopulmonary diseases in 11,480 persons. A tabulation of all diagnoses, both contributing as well as underlying causes of death, however, showed that cancer of the lung was entered upon a total of 28,123 death certificates, whereas the chronic bronchopulmonary diseases were certified as contributing to 32,041 deaths (47). The possibility that mortality data, as presently recorded, may underestimate the role of chronic bronchopulmonary diseases through incorrect listing by the physician as contributory rather than the principal cause has also been suggested (115).

Social security records in 1960 show that chronic bronchopulmonary diseases, particularly emphysema, ranked high among the conditions for which disability benefits were allowed to male workers 50 years of age or older in the United States (186).

Chronic bronchitis and emphysema are the chronic bronchopulmonary diseases of greatest public health importance in the United States. They contribute to the excess mortality of cigarette smokers, but there is little information about the effects of smoking on the other chronic bronchopulmonary diseases. The scope of the subsequent remarks is limited therefore to the possible relationship of smoking to chronic bronchitis and

emphysema. Since descriptions of both were published long before cigarette smoking became commonplace (13, 14, 114), it seems reasonable to suggest at the outset that cigarette smoking alone is not the only cause of chronic bronchitis and emphysema.

Chronic Bronchitis and Emphysema

DEFINITIONS

Many definitions of chronic bronchitis and emphysema have been suggested. For the purposes of this report the definitions proposed by the American Thoracic Society (4) will be used:

“Chronic bronchitis is a clinical disorder characterized by excessive mucous secretion in the bronchial tree. It is manifested by chronic or recurrent productive cough. Arbitrarily, these manifestations should be present on most days for a minimum of three months in the year and for not less than two successive years. Many diseases of the lung, e.g., tuberculosis, abscess, and of the bronchial tree, e.g., tumors, bronchiectasis, as well as certain cardiac diseases, may cause identical symptoms; furthermore, patients with chronic bronchitis may have other pulmonary or cardiac diseases as well. Thus, the diagnosis of chronic bronchitis can be made only by excluding these other bronchopulmonary or cardiac disorders as the sole cause for the symptoms.”

This definition and classification of chronic bronchitis later considers complications, listing three: infection, airway obstruction, and pulmonary emphysema:

“Emphysema is an anatomic alteration of the lung characterized by an abnormal enlargement of the air space distal to the terminal, non-respiratory bronchiole, accompanied by destructive changes of the alveolar walls.”

DIAGNOSIS

The diagnosis of chronic bronchitis is based essentially on descriptions of clinical manifestations and is achieved by exclusion. Recollection and interpretation on the part of the subject are necessary. There is no simple sensitive pulmonary function test that will indicate which person has chronic bronchitis.

A clinical diagnosis of emphysema, based on the clinical syndrome and certain changes in pulmonary function, is even less exact. The clinical features usually encountered in emphysema tend to be very similar to those found in chronic bronchitis. Most of the symptoms and signs and many of the physiological changes usually thought to indicate the presence of emphysema may result from airway obstruction due to bronchitis (66, 180). There is no completely satisfactory method of detecting emphysema by pulmonary function testing and no pulmonary function test is specific for the detection of pathologic lesions of emphysema (52). The clinical detection of emphysema is therefore not a simple matter, especially in the presence of chronic bronchitis.

The following, adapted from the American Thoracic Society's statement (4), epitomizes the situation for emphysema:

Clinicopathologic correlations have demonstrated that certain persons who have this morphologic alteration at autopsy have symptoms of pulmonary insufficiency during life and die of this disease. Others showing qualitatively similar pathologic findings had no respiratory symptoms during life and died of unrelated causes. In some persons, emphysema may be strongly suggested by the patient's symptoms and its existence predicted on clinical grounds with considerable accuracy. On the other hand, clinical manifestations identical with those of patients with emphysema may occur in persons who are not found to have this disease at autopsy but who have some other lung disease. Emphysema may exist without any clinical manifestations, and its clinical and functional alterations are not unique but occur in other pathologic conditions.

RELATIONSHIP BETWEEN CHRONIC BRONCHITIS AND EMPHYSEMA

Chronic bronchitis and emphysema frequently coexist, although one can be present without the other. A clinical continuum appears to extend from bronchitis at one end, through a mixture of the two conditions in the majority of cases, to emphysema at the other end (123).

An alternative method of assessing the relationship is by study of pathological change. A close relationship is found between chronic bronchitis and emphysema on purely morphologic grounds. Although emphysema occurred more frequently in patients with chronic bronchitis than could be accounted for by chance, the two conditions also occurred independently of one another (183).

Three of the possible reasons why chronic bronchitis and emphysema are found in association more often than would be expected by chance are the presence of a common cause and causation each by the other. The protective mechanisms for the upper respiratory tract are cilia and a mucous sheath, and the lower respiratory tract mechanisms involve macrophages, the lymphatic system, and possibly the fluid lining of the alveoli. Although not yet proved, failure of the protective mechanisms of the upper respiratory tract might be expected to lead to chronic bronchitis and failure of the protective mechanisms for the lower respiratory tract to emphysema. On this hypothetical basis, a common cause would not seem unlikely; noxious environmental agents in gaseous or aerosol form would be likely to affect upper and lower respiratory tracts simultaneously, perhaps with potentiation of the injury in the lower tract by particles. Several ways in which chronic bronchitis might cause or aggravate emphysema have been suggested, such as through trauma resulting from pressure changes induced in the thorax by cough (138) and by airway obstruction (114). Clinical evidence of bronchitis preceded clinical evidence of emphysema in over 50 percent of cases in one continuing study (137). Others suggest that emphysema may be a cause of chronic bronchitis (53). It seems likely that a common cause, causation of emphysema by chronic bronchitis, and causation of chronic bronchitis by emphysema are all operating mechanisms, with varying importance in different populations and different individuals (123).

Evidence Relating Smoking to Chronic Bronchitis and Emphysema

Experimental and pathological evidence bearing on the possible relationship of smoking to chronic bronchitis and emphysema has been presented in an earlier section of this chapter. Epidemiological and clinical evidence relating smoking to these diseases will be considered here.

EPIDEMIOLOGICAL EVIDENCE

Chronic bronchitis and emphysema probably represent disorders of multiple causality. Such problems are particularly suited for analysis by the epidemiological method, especially with regard to the identification of causes and the disentanglement of their relations (140). Two types of studies, prevalence studies and prospective studies, will be considered.

PREVALENCE STUDIES.—The most important epidemiological evidence available relating smoking to non-neoplastic respiratory diseases is found in the prevalence studies which concern the number of cases in a population at one point in time. The definitions and criteria for diagnosis of chronic bronchitis and emphysema are not ideal for the purposes of these epidemiological surveys. The absence of standardized diagnostic methods in chronic bronchitis and the non-specificity of clinical diagnostic criteria for emphysema have resulted in the use of prevalence of symptoms and signs of the respiratory diseases under study as a basis for the surveys.

Studies of the prevalence of chronic bronchitis and emphysema in the United Kingdom and in the United States over the last decade have developed highly reliable epidemiological methods. Because of the nature of the diseases in question, these surveys present results by the prevalence of specific symptoms and signs, or combinations, rather than diagnostic labels of disease entities. Various levels or grades of severity of the symptoms or signs are defined and the data are obtained and handled in a standardized manner, permitting comparisons between different populations and communities; thus it becomes feasible to evaluate whether smoking is associated with certain signs or symptoms to a greater extent than with other findings.

(1.) Smoking and Respiratory Symptoms—(a.) *Chronic Cough*—The common phrase “smoker’s cough” suggests that this symptom is popularly believed to be associated with smoking. Several workers have investigated the relationship between smoking and cough; Table 1 lists surveys that tabulate the frequency of cough in smokers as compared with non-smokers. Several different types of populations have been surveyed; the purpose of presenting the findings together is to demonstrate the variation found among the different populations.

The 1,456 mill workers studied by Balchum et al. (16) constituted the random sample of those who volunteered for chest X-rays and pulmonary function tests. Of 1,198 smokers, 23.3 percent reported cough; of the 253 non-smokers, 10.2 percent reported cough. When the percentage of smokers reporting cough is considered in each of several categories described by pack-years of smoking experience, a gradient was found for those reporting cough, ranging from 11 percent of those who smoked less than one pack-year of cigarettes up to 50 percent of the subjects with 60 or more pack-years of smoking experience.

TABLE 1.—Summary of reports on the prevalence of cough in relation to smoking

Author	Year	Refer- ence	Number of subjects		Percent with cough	
			Smokers	Non- smokers	Smokers	Non- smokers
Balchum	1962	(16)	1,198	253	23.3	10.2
Boucot	1962	(25)	5,331	806	31.5	13.0
Bower	1961	(26)	76	49	27.6	4.1
Densen	1963	(44)	2,530	514	21.2	7.8
Fletcher:						
London Transport	1961	(67)	272	30	20.6	0
Post Office	1961	(67)	166	10	18.7	0
Flick	1959	(68)	157	51	54.8	9.8
Olsen:						
United Kingdom	1960	(148)	162	11	32.1	0
Denmark	1960	(148)	132	24	18.9	8.3
Short	1938	(176)	1,292	496	6.4	1.6
Liebeschuetz	1959	(120)	83	52	6.0	0

Boucot and others (25) considered the relationship in older men of smoking and chronic cough in a self-selected population 45 years of age and older. Chronic cough was defined as cough existing for months or years. Again, a considerably higher percentage of the smokers reported cough, and a clear-cut gradient was established according to amount of smoking.

Bower (26) studied 172 men and women employed in a bank. This study is one of the few which included men and women working under similar conditions. Eighteen percent of 95 men and 17 percent of 77 women admitted to cough "more or less every day." Of the smokers, 27.6 percent admitted to daily cough (12 of 42 men, 9 of 34 women), whereas 4.1 percent of non-smokers admitted to this symptom (0 of 13 men, 2 of 36 women).

Densen and others (44) presented findings in transit and postal employees. Persistent cough was reported by 21.2 percent of 2,530 smokers and 7.8 percent of 514 non-smokers.

Fletcher and Tinker (67) studied male workers aged 30 to 59 in the British General Post Office and in the London Transport Executive. In the G.P.O., 18.7 percent of 166 smokers reported cough during the whole of the day in the winter, compared with none of 10 non-smokers. Among smokers of the L.T.E., 20.6 percent of 272 admitted to a comparable cough pattern whereas none of 30 non-smokers described such a cough pattern.

Flick and Paton (68) in a study of patients excluding those with cardiac and respiratory disorders, found 55 percent of 157 smokers admitted to habitual cough compared with 10 percent of 51 non-smokers. After the first hundred patients, the admission to the study was weighted in the older age groups. The questioning was not as standardized as in some of the more recent surveys.

Olsen and Gilson (148), in their study comparing findings in population samples in Britain with those in Denmark, found cough in 32.1 percent of 162 British smokers and in 18.9 percent of 132 Danish smokers; the corresponding figures for non-smokers was 0 percent of 11 and 8 percent of 24.

Schoettlin (173) studied a group of veterans in a domiciliary and medical-care center, mostly in the age group 45 to 74. The results for cough ("constantly present for two years or more") are presented in terms of

years of smoking, although the original figures were not published and are not included in Table 1. By recalculation, it appears that of those who smoked more than 10 years, 43.9 percent of 2,153 subjects had cough whereas 18.0 percent of 718 who had smoked less than 10 years had cough.

In the population samples quoted thus far, the percentage of smokers admitting to cough ranged from 17.3 percent to 55 percent, whereas the range for non-smokers was 0 percent to 13.0 percent.

Two other studies show a considerably lower prevalence of cough both among smokers and non-smokers in two unusual types of population. Short and others (176) reported the frequency with which unselected policyholders admitted to cough on periodic health examination, a time when they would be expected to minimize their symptoms. Of 1,292 smokers, 6.4 percent admitted to cough whereas 1.6 percent of non-smokers admitted to cough. In a study of a parachute brigade, Liebeschuetz (120) found 6.0 percent of 83 smokers and none of 52 non-smokers admitted to cough. The study of members of this unit with particularly high fitness standards was conducted at the time of discharge.

Hammond (82) has presented the frequency of cough in smokers and has compared this with the frequency of cough among non-smokers. The subjects were asked to state whether they had a cough at the time of the questionnaire. They were also asked the question: "Have you had a cough over a period of many years?" They also were asked to estimate its severity as slight, moderate, or severe. The analysis of complaints has been reported so far for 43,068 questionnaires, 18,697 for men and 24,371 for women. For each age group and for both sexes, cough was significantly more common among those who smoked cigarettes. The percentage with cough (and the percentage with more than a slight cough) increased rapidly with the number of cigarettes per day in both sexes and in all four age groups. Except for ex-smokers, the relationship between "chronic cough" and smoking habit was very much the same as the relationship between "present cough" and smoking habits. The proportion of male smokers with the complaint of cough was almost three times as great as might have been expected on the basis of cough prevalence among non-smokers. For women, the ratio of observed-to-expected smokers with the complaint of cough was 2.5 to 1. The ratio of observed-to-expected numbers complaining of cough "more severe than slight" was 4.09 for males and 2.74 for females. The difference in frequency of the complaint of cough or of cough "more severe than slight" between smokers and non-smokers is statistically significant at the 0.001 level. The study sample was not a random sample of the population, but it provides information about the relationship between smoking and various complaints for larger numbers of subjects than does any other study. The results again make it clear that a larger proportion of cigarette smokers are aware of cough than are non-smokers.

In each of the surveys, smoking was found to be associated with the symptom of cough defined in a variety of ways. The studied populations varied considerably—from hospital patients, workers in dusty trades and clean offices, urban and rural population samples to members of a parachute brigade. Despite the diversity of these groups, it is surprising to note the consistency of the difference between smokers and non-smokers in regard

to cough. In each of the surveys, a larger proportion of the subjects admitting to cough were smokers and about twice the proportion of smokers admitted to cough as non-smokers.

(b.) *Sputum*.—Table 2 lists surveys in which the frequency of sputum production has been tabulated separately for smokers and non-smokers in prevalence surveys. Most of the studies were considered in the section on cough and in Table 1. It is interesting that in most of these studies non-smokers report sputum production more frequently than cough.

TABLE 2.—*Summary of reports on the prevalence of sputum in relation to smoking*

Author	Year	Refer- ence	Number of subjects		Percent with sputum	
			Smokers	Non- smokers	Smokers	Non- smokers
Balchum	1962	(16)	1,198	253	30.4	11.1
Bower	1961	(26)	76	49	34.2	20.4
Densen	1963	(44)	2,530	514	21.9	13.8
Ferris:						
Males	1962	(61)	340	125	¹ 40.3	¹ 13.8
Females	1962	(61)	209	379	¹ 19.8	¹ 9.4
Fletcher:						
London Transport	1961	(67)	272	30	16.9	7.0
Post Office	1961	(67)	166	10	18.7	10.0
Flick	1959	(68)	156	49	64.7	24.5
Olsen:						
United Kingdom	1960	(148)	162	11	27.2	0
Denmark	1960	(148)	132	24	11.4	8.3

¹ Percentages standardized for age.

Ferris and Anderson (61) studied a sample of the population of a town; their results are presented as percentages, standardized for age. The sample sizes were 542 males and 695 females. Among males 40.3 percent of smokers and 13.8 percent of non-smokers admitted to sputum production with the corresponding figures for females being 19.8 percent for smokers and 9.4 percent for non-smokers.

Thus, sputum production in each of the diverse populations was found associated with smoking and a consistent difference between smokers and non-smokers was present in regard to sputum production.

(c.) *Cough and Sputum*.—The closely associated symptoms of cough and sputum have been combined in the results of a number of epidemiologic surveys. Table 3 shows the prevalence of cough and sputum in smokers and in non-smokers among samples studied.

Of particular interest is the series of comparisons made by Higgins and his colleagues (88, 90, 92, 93, 95), on samples drawn from contrasting populations, selected for their different backgrounds. Lapse rates were low, and a high degree of uniformity was achieved in the collection of information. In the disparate groups studied—including male and female subjects, older and younger, and varying in degree of dust exposure and exposure to rural or urban environment—the consistent direction and extent of the difference between prevalence rates in smokers and non-smokers demonstrates a strong relationship between smoking and productive cough in a variety of different situations, and the predominance of smoking as a determinant of these symptoms.

TABLE 3.—Summary of reports on the prevalence of cough and sputum in relation to smoking

Author	Year	Refer- ence	Number of subjects		Percent with cough and sputum	
			Smokers	Non- smokers	Smokers	Non- smokers
Higgins:						
Males	1957	(88)	222	28	23.9	7.1
Females	1957	(88)	93	176	17.2	4.5
Higgins:						
Males	1958	(93)	75	6	24.0	0
Females	1958	(93)	20	64	30.0	3.1
Higgins:						
Males	1959	(90)	315	33	29.8	6.1
Higgins:						
Males, 25-34	1959	(92)	282	56	29.1	8.9
Males, 55-64	1959	(92)	293	29	44.7	3.4
Payne:						
Males	1962	(153)	1,400	364	11.0	1.9
Females	1962	(153)	888	1,468	6.0	1.9
Phillips:						
Males	1956	(156)	823	451	51.0	2.0
Read:						
Males	1961	(159)	91	46	23.1	4.4
Females	1961	(159)	43	81	18.6	4.9
Liebeschuetz	1959	(120)	83	52	7.2	0

The percentages of symptoms noted by Oswald and Medvei (150) are unusually high because occasional cough or sputum is included, in addition to more frequent or persistent symptoms. The results are not shown in Table 3, which considers only smoking and cough *with* sputum; among males, 63.7 percent of 2,617 smokers and 47.7 percent of 985 non-smokers in Oswald and Medvei's study had cough or sputum. Among females, 63.2 percent of 970 smokers and 47.7 percent of 1,272 non-smokers admitted to either or both of these symptoms.

Payne and Kjelsberg (153) presented data on respiratory symptoms, lung function, and smoking habits in the adult population of Tecumseh, Michigan, where a comprehensive epidemiological study is being made of the entire community. Cough and sputum were graded in severity as Grade I or Grade II, the latter being defined as both cough and phlegm, of which at least one was present throughout the day for three months in the year or longer. The prevalence of Grade II symptoms is noted in Table 3. During an interview period continued for 18 months, authors were able to show that the prevalence of symptoms did not vary significantly with the season of the year. Cough and sputum at the Grade II level were admitted to by 11 percent of 1,400 cigarette-smoking males, and 2 percent of 364 non-smoking males. The corresponding figures for females were 6 percent of 888 smokers and 2 percent of 1,468 non-smokers. These Grade II symptoms increased in prevalence with advancing age in men, and in women up to 49 years. It is interesting to note that lesser degrees of cough and sputum, classed as Grade I symptoms, showed little change in frequency after 19 years of age in either sex. In both sexes, Grade I symptoms of cough and sputum were considerably more prevalent among smokers than among non-smokers—45 percent of 1,400 smokers and 19 percent of 364 non-smokers among the males, and 29 percent of 888 smokers and 17 percent of 1,468 non-smokers among the females.

Phillips and his associates (156) studied two groups: one of male employees in a steel-making plant, examined as part of an industrial hygiene program, and containing sub-groups with different types of industrial exposure, and a second group consisting of 300 patients in a Veterans Administration Hospital who were chosen at random, except for exclusion of cases of specific pulmonary diseases such as tuberculosis or tumor and cases of congestive heart failure. Chronic cough was defined as daily cough with sputum for a period of one year or more. Various possible environmental factors—geographic area, air pollution, specific work environment, and smoking—were considered. Fifty-one percent of 823 cigarette smokers were recorded as having cough, and 2 percent of 451 non-smokers. In a tabulation of chronic cough by age in decades, for cigarette smokers and non-smokers, it was shown that the increasing prevalence of chronic cough with age was much greater in the cigarette-smoking group.

Read and Selby (159) in a mixed group of 302 subjects, some of them clinic patients, some patients' friends, and some hospital staff, found that male smokers admitted to cough *or* sputum ten times as often as did male non-smokers, and to cough *and* sputum five times as often. In their female subjects the ratios for these categories were eight to one and four to one.

Liebeschuetz (120) in his study of parachute brigade members found, as might be expected, a much lower proportion of subjects with cough and sputum; these do not include subjects previously noted in Table 1 as having cough alone.

Considering these surveys as a group, it appears that the presence of cough, sputum, or the two symptoms combined, is consistently more frequent among smokers than non-smokers, in a variety of samples drawn from populations differing so widely in other respects that this association may be taken to be a general one.

TABLE 4.—*Summary of reports on the prevalence of breathlessness in relation to smoking*

Author	Year	Refer- ence	Number of subjects		Percent with breathlessness	
			Smokers	Non- smokers	Smokers	Non- smokers
Balchum.....	1962	(16)	1, 198	253	14. 5	9. 8
Densen.....	1963	(44)	2, 530	514	25. 3	16. 9
Fletcher:						
London Transport.....	1961	(67)	272	30	8. 5	0
Post Office.....	1961	(67)	166	10	9. 0	10. 0
Higgins:						
Males.....	1957	(88)	222	28	19. 8	7. 1
Females.....	1957	(88)	93	176	9. 7	19. 9
Higgins:						
Males.....	1958	(93)	75	6	29. 3	33. 3
Females.....	1958	(93)	20	64	20. 0	45. 3
Higgins:						
Males.....	1959	(90)	315	33	31. 7	18. 2
Higgins:						
Males, 25-34.....	1959	(92)	282	56	9. 9	5. 4
Males, 55-64.....	1959	(92)	293	29	42. 7	17. 2
Payne:						
Males.....	1962	(153)	1, 400	364	24. 0	12. 1
Females.....	1962	(153)	888	1, 468	29. 1	29. 0
Short.....	1938	(176)	1, 242	496	11. 5	4. 8

Some of these surveys are limited in one respect, and some in another. The degree to which bias has been avoided varies; several of the surveys quoted are open to criticism in this regard, but in others considerable pains have been taken to avoid any possibility of suggesting a relationship which may not truly exist. It would be wrong to extrapolate from, say, a hospital population to the general public, but the groups surveyed vary enough that the evidence demonstrates clearly that cigarette smokers more often report symptoms of cough, sputum, or both, than do non-smokers.

(d.) *Breathlessness*.—Table 4 summarizes the prevalence of breathlessness as reported in surveys of various populations.

Balchum and others (16) in their survey of mill workers, reported a greater prevalence of breathlessness among the smokers in their sample. Tabulation of the frequency of this complaint by pack-years of smoking experience showed a less smooth gradient than for prevalence of cough and sputum.

Densen and others (44), who studied respiratory symptoms in transit workers and postmen in New York City, found that 25.3 percent of 2,530 smokers and 16.9 percent of 514 non-smokers admitted to breathlessness of Grade II or worse (indicated by positive answers to specific questions on the questionnaire).

Fletcher and Tinker (67), in a study of Transport Executive employees and Post Office employees, had only one non-smoker out of 40 complain of breathlessness, and 38 smokers out of 438. These figures are for workers complaining of dyspnea (a positive answer to the question, "Do you have to walk slower than most people on the level?" or "Do you have to stop after a mile or so on the level at your own pace?").

In the four studies by Higgins listed in the table, the difference in prevalence of breathlessness between smokers and non-smokers is more variable. In his study (88) in the agricultural district of the Vale of Glamorgan, the author presents prevalence figures for the various symptoms among females in two age groups, those under age 45, and those over age 45. His reason for doing so is the considerable difference in frequency of the smoking habit between women in these two age-groups. In both the age groups of females, the prevalence of breathlessness is greater among the non-smokers, but the difference is not statistically significant. Female smokers in the over 45 age groups have rather more cough and sputum and wheeze than the non-smokers, but apparently have less breathlessness. In his study in Annandale (93) the prevalence of breathlessness among all men and all women studied was greater in the non-smokers than in the smokers, although the numbers of non-smoking men and of smoking women were small. When males aged 55 to 64 are considered, from the three surveys (90), breathlessness is more prevalent among the smokers, and the same thing applies to the two different age groups of males studied in Staveley (92).

Payne and Kjelsberg (153), in their survey of a total community, have stated that among the men, cigarette smokers were affected more often with breathlessness at all ages. Among the women, cigarette-smokers had a higher prevalence of breathlessness than non-smokers below the age of 40, and above this age the non-smokers had a higher prevalence. Considering all ages together, twice the proportion of male smokers admitted shortness of breath

compared to non-smoking males; the prevalence of shortness of breath among females was the same for smokers and non-smokers.

Short et al. (176), in a study of answers to a questionnaire on routine medical examination for insurance purposes, obtained a larger percentage of complaints of breathlessness among smokers than among non-smokers.

Hammond (82) also presents figures for the frequency with which breathlessness was noted in answer to a questionnaire by 18,697 men and 24,371 women. The relationship between breathlessness and smoking is less clear than the relationship between cough and smoking. A significantly greater proportion of complaints of breathlessness was encountered among male and female cigarette smokers, both for total complaint of breathlessness and complaint of breathlessness "more severe than slight." The ratio of observed-to-expected complaints of breathlessness among male smokers was 1.97 for the total number with this complaint, and 2.62 for those complaining of breathlessness more severe than slight. The ratios for females were 1.36 and 1.49. A consideration of the frequency of complaints of shortness of breath in smokers and in non-smokers, by age group and by sex, shows that the excess of breathlessness among cigarette smokers is greater and more consistent for men than for women. The older age groups of women show only a slight excess.

Thus, the relationship between smoking and the symptom of breathlessness is less general than the relationship between smoking and cough or sputum, which is found in all age-sex groups in a variety of different populations. For males the association is clear; male cigarette smokers complain of breathlessness more often than do non-smokers, particularly in the older age groups. Females present a less uniform pattern. In several surveys, females show a higher prevalence of breathlessness in non-smokers than in smokers, particularly in the older age-groups. The reasons for this sex difference have not been explained.

(e.) *Smoking and Chest Illness.*—The percentage of smokers and non-smokers who reported chest illness in the three years prior to the interview

TABLE 5.—*Summary of reports on history of chest illness in the past 3 years in relation to smoking*

Author	Year	Refer- ence	Number of subjects		Percent with chest illness	
			Smokers	Non- smokers	Smokers	Non- smokers
Fletcher, London Transport	1961	(67)	272	30	9.2	4.3
Post Office	1961	(67)	166	10	33.7	20.0
Higgins: Males	1957	(88)	222	28	17.1	3.6
Females	1957	(88)	93	176	15.1	13.1
Higgins: Males	1958	(93)	75	6	16.0	0
Females	1958	(93)	20	64	10.0	10.9
Higgins: Males	1959	(90)	315	33	23.8	3.0
Males, 25-34	1959	(92)	282	56	12.8	7.1
Males, 55-64	1959	(92)	293	29	27.3	6.9
Payne: Males	1962	(153)	1,400	364	11.0	9.1
Females	1962	(153)	888	1,468	16.0	13.0

date is presented in Table 5. For men, the prevalence was consistently higher among smokers, and in one study (93), the association of smoking and chest illness was apparent for the younger (25-34) as well as the older males (55-64). For female smokers and non-smokers, the prevalence of chest illness was about the same.

(f.) *Combinations of Symptoms.*—A number of prevalence studies (7, 54, 61, 62, 77, 150) have reported results, either totally or in part, under diagnostic headings which cannot be translated into single symptoms. The symptom combinations and the names applied to them varied; some of the studies gave the percentages of smokers and non-smokers with “any” signs or symptoms rather than specified combinations. The results are presented in Table 6.

TABLE 6.—*Summary of reports on the prevalence of combinations of certain symptoms in relation to smoking*

Author	Year	Refer- ence	Number of subjects		Percent with symptoms	
			Smokers	Non- smokers	Smokers	Non- smokers
Ashford	1961	(7)	3,214	677	21.7	10.3
Edwards	1959	(54)	779	524	29.4	19.5
Ferris:						
Males	1962	(61)	340	125	¹ 24.9	¹ 7.3
Females	1962	(61)	209	379	¹ 17.5	¹ 9.4
Ferris:						
Males	1962	(62)	54	20	42.6	15.0
Females	1962	(62)	10	60	20.0	10.0
Goldsmith	1962	(77)	1,238	744	43.0	31.4
Oswald:						
Males	1955	(150)	2,617	985	16.1	9.7
Females	1955	(150)	970	1,272	15.4	9.1

¹Percentages standardized for age.

Ashford and his colleagues (7) found twice the proportion of “respiratory symptoms” among Scottish coal mine workers who smoked than among those who did not smoke. “Respiratory symptoms” were regarded as present in those who have cough or sputum all day for more than three months per year *and* walk slower than others on the level, or wheeze, or if the weather affects their chest, or if they have had a chest illness in the last three years. Those who had wheeze and who claimed the weather affected their chest were also classed under “respiratory symptoms.”

Edwards and others (54) presented the percentage of smokers and non-smokers with bronchitis, according to clinical assessment by one of 11 general practitioners cooperating in the survey. No attempt to standardize the diagnosis was reported. Of 779 smokers, 29.4 percent had “bronchitis” compared with 19.5 percent of 524 non-smokers.

Ferris and Anderson (61) presented the prevalence of “irreversible obstructive lung disease,” which was defined as the report that wheezing or whistling in the chest occurred most days and nights, that the subject had to stop for breath when walking at his own pace on the level, or had a forced expiratory volume in the first second of expiration (F.E.V. 1.0) of less than 60 percent of the total forced expiratory volume. According to this definition, male smokers showed a 24.9 percent prevalence of irreversible

obstructive lung disease, compared with 7.3 percent of male non-smokers. The corresponding percentages for females were 17.5 percent and 9.4 percent. These percentages were age-standardized.

In a study conducted in a flax mill, Ferris, et al (62) presented the prevalence of "chronic respiratory disease," defined as productive cough on four days of the week, for three months of the year, for three successive years; or wheezing in the chest most days and nights; or breathlessness, of Grade III or more, in the winter; or asthma diagnosed by the physician at the time of the survey; or F.E.V. 1.0 less than 60 percent of forced vital capacity. Under this definition, 42.6 percent of 54 male smokers and 15.0 percent of 20 male non-smokers had "chronic respiratory disease." For females, the figures were 10.0 percent of 10 smokers and 10.0 percent of 60 non-smokers.

Goldsmith and others (77), in their study of longshoremen, classified the subject as having a "respiratory condition" if he had ever had asthma or bronchitis, or currently was "troubled by constant coughing." With this definition, 43.0 percent of 1,238 moderate or heavy smokers had a respiratory condition, compared with 31.4 percent of 744 non-smokers.

Oswald and Medvei (150), defining "bronchitis" as disability from acute exacerbations of chest symptoms, or breathlessness, or both, found a prevalence of 16.1 percent among 2,617 male smokers, and of 9.7 percent among 985 non-smokers. In their female subjects, 15.4 percent of 970 smokers compared with 9.1 percent of 1,272 non-smokers had "bronchitis."

Although these various combinations of symptoms are not comparable, the consistency and extent of the differences between prevalence of symptom combinations in smokers and non-smokers are striking.

(g.) *Relationship between Symptoms or Signs and Amount Smoked.*—In several surveys, smoking categories were based on the daily consumption or total lifetime consumption (16, 61, 67, 82, 90, 153). In the majority, the prevalence of cough and sputum increased with amount smoked. A recent study (82) showed that those who smoked cigarettes of low nicotine content tended to cough less than those who smoked cigarettes of high nicotine content. Other symptoms and measurements of pulmonary function show a less clear relationship between prevalence and amount smoked.

(h.) *Relationship between Symptoms and Signs and Method of Smoking.*—The numbers of pipe and cigar smokers in many prevalence studies are so small that conclusions about the effects of these methods of smoking are not reliable, but they all tend to show that pipe and cigar smokers are likely to be intermediate between non-smokers and cigarette smokers in prevalence of symptoms and signs.

(i.) *Ventilatory Function.*—Pulmonary tests and the method of presenting results, though varying widely, are important features of the prevalence surveys.

In the study by Ashford and others (7) of 4,014 coal miners, the forced expiratory volume in the first second of expiration (F.E.V. 1.0) of non-smokers was slightly higher than that of the smokers, and a small but statistically significant difference was found even after correction for differences attributable to physique. No consistent relationship was reported between the amount smoked and the average F.E.V. 1.0.

Balchum and others (16) reported that 19.3 percent of 1,194 smokers and 7.8 percent of 243 non-smokers had an "abnormal" test, an F.E.V. 1.0 of less than 70 percent. When the "abnormal" test was compared with the number of pack-years of cigarettes smoked, a steady increase in the proportion of men with decreased F.E.V. 1.0 was found with increasing pack-years.

Ferris and Anderson (61) showed a progressive decrease in the mean F.E.V. 1.0 in successive age groups for male smokers, male non-smokers, and female non-smokers. In males, there was also a regular decrease in F.E.V. 1.0 within each age group with increase in the number of cigarettes currently smoked. In females, there was little difference in the F.E.V. 1.0 between smokers and non-smokers except in one age group. The peak expiratory flow rate showed a decrease with age and a decrease within the age groups with cigarette smoking.

Chivers (36) showed that smoking, age, and height were correlated significantly with the expiratory flow rate. The older and shorter men had greater impairment associated with smoking.

Flick and Paton (68) demonstrated a distinct decline, beginning at about 40 years of age, in expiratory flow rate among smokers, but no apparent change among non-smokers until 70 years of age.

Fletcher and Tinker (67), measuring expiratory flow rates by the Peak Flow Meter, found one group of smokers, but not another, had lower values than the non-smokers. In a later paper (58), Fairbairn, Fletcher and Tinker reported that the Peak Flow Meter appeared to be a less satisfactory screening test than the forced expiratory volume.

Franklin and Lowell (73), in a study of 1,000 apparently healthy factory workers, found the mean expiratory flow rate during the third quarter of maximal forced expiration to be approximately 20 percent less in "heavy smokers" than in "light smokers." "Heavy smokers" were defined as those who had smoked 30 pack-years or more, and "light smokers" less than 10 pack-years.

Higgins (88) showed a decrease in F.E.V. 0.75 among smokers of 15 grams or more of tobacco per day, compared with non-smokers and with those who smoked less than 15 grams a day. For this test, there was no significant difference between non-smokers and the lighter smoking group. Peak flow measurements indicated a difference between heavy and light smokers, and also between non-smokers and light smokers. In each 10-year age group over 45, the peak flow was lower in smokers than in non-smokers, but the numbers were small. These differences are not explained by differences in age, social class, or occupation. The difference between smokers and non-smokers in peak flow measurement was not seen in tests of women.

Higgins (90) summarized the difference in F.E.V. 0.75 in a variety of different samples of the population. Tabulations for 16 different groups included miners and ex-miners in varying pneumoconiosis categories and non-miners in the same district, and agricultural workers in two different areas in Britain. In the 13 groups in which comparisons were feasible, non-smokers recorded a higher F.E.V. 0.75 than the smokers. The small over-all difference in means was recorded (as indirect Maximum Breathing Capacity) as 50 liters per minute, which was significant at the one percent

level. By pooling subjects with different occupations in the older age groups, differences between light and heavy smokers were apparent, though not statistically significant. Higgins commented on a strong trend in the prevalence of persistent cough and sputum, with amount of tobacco smoked, without a significant trend in ventilatory capacity. His possible explanation of the difference is that smokers are more likely to give up smoking or reduce the amount smoked, once their lung efficiency becomes impaired, than they are when their only symptoms are cough and sputum.

In their study of miners and foundry workers in Staveley (92), Higgins and his colleagues showed a decrease in the F.E.V. 0.75 in smokers. Non-smokers, light smokers, and heavy smokers (15 grams per day and over) ranked in that order for decreasing F.E.V. 0.75, both in men aged 25 to 34 and in those aged 55 to 64. The difference between the non-smokers and the light smokers was smaller than the difference between the light and the heavy smokers in the younger age group; in the older age group the difference was larger between non-smokers and light smokers.

Olsen and Gilson (148) measured the F.E.V. 0.75 in a sample of a population in Denmark for comparison with British population samples. Cigarette smokers had a lower mean F.E.V. 0.75 than cigar smokers or pipe smokers who in turn had a higher mean than non-smokers, but these differences were not statistically significant. If non-smokers, cigar smokers, and pipe smokers are grouped together, non-cigarette smokers had a significantly higher mean F.E.V. 0.75 than the cigarette smokers.

Payne and Kjelsberg (153), who presented mean values of F.E.V. 1.0 for men and women by age group and by smoking category, found a lower mean value for cigarette smokers than for non-smokers in each age group of men over 19. In the 16-to-19 age group, cigarette smokers had a slightly higher mean value than non-smokers. A comparison of the mean values by age group for non-smokers and for cigarette smokers shows a decline with advancing years in both, but more rapid in the cigarette smokers. Women also show a decline of F.E.V. 1.0 with advancing years, but this is no more marked and no more rapid in the cigarette smokers than in the non-smokers. The reduction in F.E.V. 1.0 in cigarette smokers amounted to 7 percent and 3 percent of the mean values in non-smoking men and women respectively when values adjusted to the over-all mean age of 40 years were compared.

Read and Selby (159) measured peak flow rates in smokers with cough, and in smokers with cough and sputum. To a statistically significant extent, male smokers without cough or sputum showed a more rapid fall in peak flow rate with age than expected. Male smokers with cough showed a still more rapid fall with age, and those with cough and sputum, the most rapid fall. Amount smoked had no obvious effect. Results were similar for women.

Revotskie and his colleagues (165), who grouped smokers in Framingham as never smoked, light smoker, medium smoker, and heavy smoker, found that the F.E.V. 1.0 measurements show a gradient from never smoked to heavy smoker in the "normal" subjects, both for males and females; in the other groups this gradient is not clear. The "Puffmeter" ratios tended in the same direction, but in less clear-cut fashion than the F.E.V. 1.0 measurements.

Goldsmith and others (77) showed that smokers, regardless of amount smoked, have a slight diminution in the pulmonary function test results, even in the absence of respiratory symptoms. The total vital capacity was much less sensitive in this regard than the F.E.V. 1.0 or the "Puffmeter" reading. Longshoremen with "respiratory conditions," and particularly those with shortness of breath, had a more marked decrease in pulmonary function. Cough was associated with the greatest diminution of pulmonary function measurement.

The relationship between cigarette smoking and abnormal results of pulmonary function tests is more difficult to evaluate from the published surveys than is the relationship between symptoms and cigarette smoking. Pulmonary function test results are influenced by several factors, among which are age, physique, and perhaps occupation. When allowance is made for these factors, there appears to be a clear difference in the ventilatory function between smokers and non-smokers.

In the majority of prevalence surveys, the subjects were not forbidden to smoke prior to pulmonary function testing. Since acute alterations due to smoking might be misinterpreted as due to a permanent abnormality, it is important to examine the magnitude and significance of the acute effects of smoking on pulmonary function.

Bickerman and Barach (20) found no consistent alterations in vital capacity or in maximum breathing capacity before and after their patients and normal subjects smoked three cigarettes. Simonsson (177) found a small decrease in the F.E.V. 1.0 in 13 of 16 young subjects after smoking, and the difference for the group was statistically significant. No significant change was found in the total capacity.

Several authors have studied more sensitive tests of airway resistance and lung compliance. Eich, Gilbert and Auchincloss (56) made compliance and airway resistance measurements, using an esophageal balloon technique, on a group of nine healthy adults, five of whom had respiratory symptoms. No difference was detected after one cigarette. In a group of emphysematous patients, a statistically significant increase in airflow resistance was found, but without significant change in compliance.

Attinger and others (8) reported no statistically significant difference in expiratory airflow resistance or compliance, but in a later study of subjects with pulmonary disease, significant physiological changes—increased mechanical resistance and increased work of breathing—were noted after smoking one or two cigarettes.

Motley and Kuzman (142) studied the lung volumes, spirometry, blood gas exchange, and pulmonary compliance in 141 subjects, before and after smoking two cigarettes. Not all of these measurements were made on all subjects. There was no significant change in the mean values of vital capacity performed after smoking, some subjects showing a decrease, and others an increase. Six of the normal subjects showed a decreased compliance after smoking. In 33 subjects with cardiac or respiratory disease, 17 had a significant decrease in compliance after smoking. The authors felt that a decrease in pulmonary compliance was the only notable abnormality which followed smoking acutely. Forced expiratory volume and airflow resistance studies were not included.

Miller (134a), who constructed pressure-volume work loops, demonstrated increased airflow resistance and uneven ventilation, resulting in increased work of breathing. This author concluded that inhalation of cigarette smoke gives rise to a significant degree of uneven ventilation, which is responsible for the observed decrease in dynamic compliance and increased elastic work of breathing.

Nadel and Comroe (146) showed a mean decrease of 31 percent in the ratio of airway conductance to thoracic gas volume after inhalation of cigarette smoke, the changes being highly significant statistically, and similar for smokers and non-smokers. Repeated testing after smoking showed the response to last for from 10 to 80 minutes. Without inhalation, no significant change in the conductance to thoracic gas volume ratio occurred. Inhalation of Isuprel aerosol before smoking prevented the increase in airway resistance, and when given after cigarette smoking it counteracted the increase.

Zamel, Youssef, and Prime (194) found that the smoking of one cigarette increased airway resistance in smokers and non-smokers, and that the inhalation of Isuprel reduced airway resistance in both groups. The authors comment that the difference in airway resistance between non-smokers and cigarette smokers is apparent only when the actual estimates of airway resistance are compared with predicted values based on lung volume, because of a reciprocal relationship between airway resistance and lung volume. They add that the experimental values for airway resistance in two groups of persons are not comparable unless allowance is made for the volume of the lungs in each.

To sum up this point, the acute effects of cigarette smoking upon pulmonary function are expressed mainly through increase in airway resistance, which is not severe enough to produce clinically evident manifestations. The smoker is not immediately aware of any increased difficulty in breathing nor are the pulmonary function tests used in surveys sufficiently sensitive to detect the acute effects. The differences in results of pulmonary function tests between smokers and non-smokers, therefore, are greater than can be accounted for by acute effects from a recently smoked cigarette.

PROSPECTIVE STUDIES.—In six of seven prospective studies, chronic bronchitis and emphysema contribute markedly to the excess mortality among cigarette smokers; in the remaining study the mortality ratio was increased but to a lesser extent. In all these studies, mortality ratios for chronic bronchitis and emphysema have been calculated (see Tables 19, 23, 26 in Chapter 8, Mortality). Cigarette smokers in these studies died of chronic bronchitis and emphysema 6.1 times more frequently than non-smokers.

In the large study of U.S. veterans (49) the observed number of deaths among smokers attributed to chronic bronchitis was 26 whereas the expected number based on deaths among non-smokers was 5.6, or a mortality ratio of 4.6. For emphysema, the observed number of deaths among smokers was 115, whereas the expected number was 8.8, or a mortality ratio of 13.1.

In a recent study (82), information is available on the first 22 months of follow-up of 447,831 men between the ages of 35 and 89, of whom 11,612 have died. The observed number of deaths attributed to emphysema in cigarette smokers was 115 whereas the expected number was 15.4; the mortality ratio was 7.47. For other pulmonary diseases the mortality ratio was 1.65, with 185 observed deaths in smokers as compared with 112.7 expected deaths. The duration of follow-up is not yet sufficiently long to allow one to expect deaths from chronic bronchopulmonary disease in persons who were not afflicted at entry.

The paucity of published morbidity studies is striking. Very little is known of the progression in population samples of symptoms or signs related to chronic bronchitis or emphysema, or found in smokers more frequently than in non-smokers. And very little is known of the incidence rates of such symptoms and signs in the different categories of subjects constituting population samples. This is unfortunate, as prospective studies of morbidity in population samples can best measure the possible health hazard of smoking. Several studies are under way, but some of the important information will concern changes occurring over a period of five years or more.

The only study of this type reported so far is by Higgins and Oldham (94), who measured the F.E.V. 0.75 in a five-year follow-up study on ventilatory capacity in a population sample in a mining district in Wales. In non-miners this measurement fell more over the five years in smokers than in non-smokers, and within the smoking group there was an increasing fall with amount of smoking. When the miners and ex-miners were considered.

the pattern was less clear. In three of the four groups, the F.E.V. 0.75 of the smokers fell more than that of the non-smokers or ex-smokers; but the fall was usually greater in the light than in the heavy smoking group. The authors pointed out that when the original sample was selected, no follow-up was intended, and that the sample was not very suitable for this purpose.

Thus, morbidity data are insufficient at present to be of value in the estimation of the possible health hazard of smoking. Prospective studies in populations followed over long periods offer the best opportunity for filling the major gaps in knowledge about the relationships of smoking and chronic bronchopulmonary diseases.

CLINICAL EVIDENCE

Several studies concerned with individual patients rather than defined populations form the basis for the clinical evidence.

A current and continuing study of an "emphysema registry" with entry based on clinical and physiological evidence, has been reported (138). Of 131 patients with diffuse pulmonary emphysema, 20 had findings at necropsy of widespread alveolar destruction. Clinical differentiation was made into three groups: a "bronchitic" group in whom a history of cough was present years before onset of dyspnea on exertion, a "dyspneic" group in whom cough and dyspnea occurred at about the same time or in whom dyspnea occurred first, and an "asthmatic" group who gave a history of episodic dyspnea or asthma for years before the onset of uninterrupted dyspnea. When the sample of patients was adjusted for age and sex, 95 percent were smokers as compared with an expected 80 percent based on smoking habits of Americans. In a later report (137), the number of patients had increased to 150; 99 percent of the "bronchitic" group, 98 percent of the "dyspneic" group, and 79 percent of the "asthmatic" group were cigarette smokers. Improvement occurred in 70 percent of the 60 patients who stopped smoking, as compared with 1 percent of the 84 patients who continued smoking.

Studies of series of patients by others (1, 125) have also noted the frequent association of cigarette smoking with emphysema. A number of clinical studies indicate the frequent association of cigarette smoking in chronic bronchitis (106, 117, 149). Fewer non-smokers were among the bronchitis patients than in matched controls in two of the studies (117, 149). Of interest is a comparison of 127 cases of chronic bronchitis with a similar number of controls (75); no difference in smoking habits was found in the men, and very little difference in the women.

On the basis of such studies, with varying diagnostic criteria, several authors have concluded that cigarette smoking may be an etiologic factor in chronic bronchitis and emphysema. Most but not all of the studies have shown smoking to be a more common habit among the bronchitis or emphysema patients than among the control groups. Such evidence can do little more than provide a basis for hypothesis and indicate the effect of continued smoking on established disease; it does not, of course, establish or exclude a causal relationship.

Relationship of Smoking, Environmental Factors, and Chronic Respiratory Disease

ATMOSPHERIC POLLUTION

BASIS FOR INTERRELATIONSHIP AND RELATIVE MAGNITUDE OF EXPOSURE—
(1.) **Experimental Evidence.**—The threshold level below which chronic exposure to a toxic agent fails to produce damage to the respiratory system has not been established even for many of the known components of tobacco smoke and atmospheric pollution. It is known, however, that the mechanism by which inhaled substances produce an irritant response in the lung is not a simple one. Physical, chemical, and biologic interaction may result from multiple, simultaneous exposure to a wide variety of the components. Potentiation of the irritative action of certain gases when inhaled together with an aerosol of small particles has been demonstrated (5, 113, 152). A possible example of potentiation may be found by contrast of two natural atmospheric pollution disasters; the 1962 London smog episode had lower particulate levels, approximately equivalent sulfur dioxide levels, and fewer deaths than the 1952 London smog.

Innumerable components with potential biologic effects are present in tobacco smoke and as atmospheric pollution; some components are common to both. At present, information concerning the effects on the respiratory system is available for relatively few of these components. In an earlier chapter of this report (Chapter 6), the toxic actions of the particulate phase and major gas constituents of cigarette smoke are discussed; nitrogen dioxide, and to a much lesser extent, formaldehyde, are the gas components capable of producing pulmonary lesions related to respiratory disease of man. The components which constitute pollutants in ambient air vary widely, largely because of differences in source, meteorologic variables, and photochemical interactions. The effects of some of the major gas constituents in air pollution upon the respiratory system are known and will be presented briefly.

Sulfur dioxide is rapidly absorbed into the lung but removed slowly, persisting for one week after a single exposure (15). Interference with the clearance mechanism is produced through effects upon the mucus, rather than by inhibition of ciliary motility as seen with cigarette smoke.

Sulphur dioxide usually exerts its effects upon the upper bronchial tree but intensive, protracted exposure may result in damage to the more distal airways. In animals, short-term, high-level exposures result in increased airflow resistance, and hypersecretion of mucus has been suggested by changes in the mucosa after moderately high, intermittent exposure of guinea pigs for six weeks (162). Chronic low-level sulfur dioxide exposures have produced fibrotic bronchitis (86). Experimental human exposures confirm the increased airflow resistance which may occur without symptoms; augmentation of the effects of sulfur dioxide in the presence of particulates also has been observed in humans but it was less evident than in guinea pigs (72, 76, 193).

Ozone produces irritant actions on the respiratory tract much deeper in the lung than sulfur dioxide. Repeated inhalation of 1 ppm. produces chronic bronchitis and bronchiolitis in rodents, especially rats, but no detectable ef-

fects are produced in dogs (179). Under conditions of acute exposure, somewhat more than 1 ppm. of ozone produced increased airway resistance and decreased diffusing capacity in man (76). It is not known whether chronic low-level exposure to ozone produces lung damage in man.

The ingredients of motor vehicle exhausts most likely to have biologic effects are aldehydes, hydrocarbons, oxides of nitrogen, and carbon monoxide. Guinea pigs exposed to ultra-violet irradiated exhaust gases have enhanced susceptibility to infection and bronchospasm (2, 144). No data are available on the long-term inhalation of low concentrations of irradiated exhaust gases or photochemical smog and its effects on human pulmonary tissues.

At present, it has not been demonstrated that other components common in air pollution are associated with pulmonary lesions similar to those found in the chronic respiratory diseases of man.

(2.) Relative Magnitude of the Exposure.—Estimates of the relative magnitude of exposure to constituents common to both cigarette smoke and atmospheric pollution are made difficult by the complex nature of the characteristics of the exposure, such as the relationship between concentration and duration, and by the paucity of studies specifically designed to evaluate this aspect. In general, levels are likely to be high, brief, and frequently repeated in the discontinuous exposure to cigarette smoke; air pollutant exposure may be considered to be relatively continuous but with wide variation in concentration and composition, particularly in the United States.

The relative magnitude of each type of exposure cannot be accurately calculated at present. Insight may be gained, however, into the relative magnitude of exposure to two components, carbon monoxide and the oxides of nitrogen, common to cigarette smoke and atmospheric pollution. The smoking of 30 cigarettes per day is estimated to provide a 20- to 25-fold greater exposure to carbon monoxide than would be experienced in the ambient air of Pasadena by non-smokers (76). The effect of smoking on carboxyhemoglobin levels in man has been determined in studies utilizing carbon monoxide in air expired by cigarette smokers and non-smokers with similar high level community atmospheric pollution exposure. The effect of cigarette smoking on carboxyhemoglobin levels in man was more than five times greater than the effect of atmospheric pollution, even when the studies were performed in a relatively heavily polluted area (76).

The relative magnitude of exposure to the oxides of nitrogen may also be estimated for cigarette smoking as compared with atmospheric pollution. The average concentration of nitrogen oxides in ambient air is 0.3 ppm. in the Fall quarter in downtown Los Angeles. The oxides of nitrogen present in cigarette smoke vary from 145 to 665 ppm.; moreover, virtually complete absorption occurs after inhalation (23). During periods of cigarette smoking, therefore, a substantially greater exposure to nitrogen oxides would be expected (76).

Since cigarette smoking is likely to occur on every day of the year and periodically throughout the day and evening, and community air pollution is likely to be relatively less common or persistent, the relative magnitude of the effect of cigarette smoking for the bulk of the United States population is certain to be greater than indicated above. The exact magnitude is per-

haps less important than the finding that it is substantially greater (76). Thus, using exposure either to oxides of nitrogen or carbon monoxide as an index, substantially greater exposure results from cigarette smoking than from atmospheric pollution, even when studies are conducted in a highly polluted atmosphere in the United States. Whereas estimates of exposure to many other constituents of both types of pollution will be necessary before the relative hazard can be calculated more fully, the experimental evidence at present is consistent and indicates that cigarette smoking affords the greater exposure for the bulk of the population of the United States.

EPIDEMIOLOGICAL EVIDENCE.—Most investigations of epidemiologic design have not been directed toward determination of the relative importance, or the combined effects, of cigarette smoking and atmospheric pollution in chronic respiratory disease. Discernible effects of cigarette smoking, such as cough and sputum production, have been observed and documented in the presence or absence of atmospheric pollution. A detailed consideration of the epidemiological data is available (76); only selected studies will be considered here.

The prevalence of cough and sputum in the United States appears to be determined much more by the amount and duration of cigarette smoking than by atmospheric pollution. In comparable samples of cigarette smokers in New York, Baltimore, Los Angeles, and San Francisco no major differences were found in the prevalence of cough and sputum (76, 101); it is interesting that similar results were obtained comparing cigarette smokers in London, England and Bergen, Norway (139). Atmospheric pollution had little or no detectable effect on the prevalence of respiratory disease among residents of a New Hampshire town; a substantially greater prevalence of chronic nonspecific respiratory disease was present, however, in cigarette smokers than in non-smokers of similar age and sex (6, 61). In veterans paired by age and smoking history, the frequency of respiratory symptoms and alterations in pulmonary function tests correlated well with past cigarette smoking history; in contrast, study of these men during the season in which Los Angeles atmospheric pollution was high did not result in detectable response attributable to the atmospheric pollution (173). In studies in areas with varying severity of atmospheric pollution, the effects of cigarette smoking have been observed (16, 77, 165). Pulmonary emphysema is relatively rare in a population of non-smokers who live mostly in the areas of California with greatest atmospheric pollution (51).

In the United Kingdom, cigarette smoking and atmospheric pollution both contribute to the development and progression of chronic bronchopulmonary disease (28). Chronic bronchitis results in a mortality rate 30 to 40 times higher in both sexes and at all ages than is seen in the United States. The excess mortality remains even after removal of possible differences in classification and misinterpreted diagnosis (63). Moreover, differences in tobacco consumption do not appear to be sufficiently large to account for the excess mortality due to bronchitis in the United Kingdom.

In producing simple, uncomplicated bronchitis, cigarette smoking appears to have the same result in the two countries (63). Although recurrent chest illness and evidence of airway obstruction are more frequent in cigarette smokers, the frequency of more advanced forms of chronic bronchitis does

not increase with increasingly heavy smoking (65). Atmospheric pollution in the United Kingdom exerts its effects primarily among chronic bronchitics (117) almost all of whom are cigarette smokers (64); it also is a major factor in the urban-rural differences in prevalence and mortality (37, 65, 154, 160). When those findings are considered together with other evidence documenting the role of atmospheric pollution in chronic bronchitis (28, 76, 161), it seems probable that atmospheric pollution and cigarette smoking in the United Kingdom are at least additive and possibly synergistic in their deleterious effect on the respiratory tract.

Thus the epidemiological evidence on the relationship of cigarette smoking, atmospheric pollution, and chronic respiratory disease clearly indicates that the dominant association in the United States is between cigarette smoking and chronic respiratory disease. In the United Kingdom, disabling respiratory conditions and death are more likely to occur among persons who smoke cigarettes and are exposed frequently to atmospheric pollutant than in those exposed to either alone.

OCCUPATIONAL FACTORS

Occupational exposures provide other possible etiologic factors in the production of chronic bronchitis and emphysema. There is little convincing evidence on specific relationships. Nevertheless, epidemiological studies (reviewed in 123, 128) provide information on the relative importance of cigarette smoking and occupational exposures in selected groups.

In a study of 4,014 Scottish coal miners (7), the prevalence of respiratory symptoms among non-smokers was appreciably lower than among smokers of the same age, and the ventilatory function of non-smokers in all age groups was significantly higher than that of the smokers. Among smokers of 50 years of age and above, the prevalence of pneumoconiosis tended to be lowest among the men who smoked the most and highest among men who smoked the least. However, the prevalence of pneumoconiosis was higher in ex-smokers than among smokers and non-smokers, except in the oldest age group, suggesting that men with pneumoconiosis tend to reduce their tobacco consumption. The possibility that factors of selection eliminate some persons with symptomatic pneumoconiosis from study groups should also be considered in the evaluation of these studies.

In a sample of 1,317 men aged 40 to 65 who worked in a variety of non-dusty and dusty environments, a greater prevalence of bronchitis (daily cough for at least the preceding six months, productive of one teaspoon of sputum per day) was found in moderate and heavy smokers (27). Between the non-smokers and the heavy smokers, a significant difference was found at all age levels, and also between non-smokers and moderate smokers except in the oldest age group. Although effects from dust exposures could be noted, it appeared that cigarette smoking was the dominant etiologic factor in "chronic bronchitis" in this selected group.

Among alkaline dust workers it was found that the dusts in the working environment did cause some increase in respiratory illness but the significance of the dusts in the production of respiratory disability, either functional or pathological, was not as important as the number of cigarettes smoked daily (36).

In a study of 1,274 steel workers, non-smokers had a comparatively low incidence of chronic cough, regardless of their job classification or conditions of work or residence. There was a direct relationship between chronic cough and the number of cigarettes smoked daily in each occupational category (156). Cigarette smoking was of greater importance in determining the prevalence of chronic cough than was the occupational exposure.

In a study of New England flax mill workers, 161 subjects were subjected to a questionnaire and measurements of pulmonary function to determine the presence of "chronic non-specific respiratory disease." The prevalence of such a syndrome, based on a certain combination of symptoms or signs, was related to age, sex, smoking habits, years of exposure to dust, and estimated inhaled quantity of dust. The effect of smoking "far out-shadows any effect due to age or occupational exposure to dust" (62).

The studies by Higgins and his colleagues (87, 88, 89, 91, 92) show that smoking and occupational exposure are both related to the prevalence of chronic respiratory disease but do not allow quantitative assessment of their relative importance in the populations defined. As this series of studies was undertaken to demonstrate any effect from industrial exposure, and the populations surveyed were such that exposure to occupational dusts was more varied than in the general population, the importance of the effect of smoking in this group of studies on the production of respiratory symptoms is rather convincing (123). The authors comment in one of the papers in this series: "So important is the influence of tobacco smoking that it is essential to allow for differences in smoking in comparable groups before drawing conclusions about the importance of other factors."

In a recent study of bituminous coal miners (103), ex-smokers had pulmonary function results and prevalence of respiratory symptoms comparable to those of non-smokers; no impairment was attributed to pure pipe or cigar smoking. Cigarette smokers had the most symptoms of respiratory disease and, except for vital capacity, they had the lowest pulmonary function. The authors comment: ". . . although smoking definitely impairs pulmonary function, the impairment of pulmonary function by years worked underground is clear and separate from the effect of smoking."

In a study of 7,404 metal mine workers, aged 35 years and older, a comparison was made of the effects of 20 years' aging and smoking on pulmonary ventilation, as measured by the F.E.V. 1.0 in individuals without X-ray evidence of silicosis. A decrease of 23 percent occurred with the process of aging 20 years. For heavy smokers (those who smoked for 25 years or more and now smoke more than 20 cigarettes a day), there was an additional decline of 10 percent over that of aging alone. "The decline in pulmonary function associated with heavy smoking was equivalent to the decline that comes about by the process of aging 10 years. For the entire group of metal mine workers, the reduction in pulmonary function associated with smoking was equivalent to half the effect of heavy smoking, or about five years of aging" (128).

The population at risk from occupational exposure is relatively small compared to the population of cigarette smokers. Among occupational groups, cigarette smoking is an important variable that must be considered in all

studies of chronic bronchopulmonary disease. In most studies, but not all, the relative importance of cigarette smoking is greater than occupational exposures in the production of symptoms and signs of chronic bronchitis or emphysema.

SUMMARY

Tobacco smoke is a heterogenous mixture of a vast number of compounds, several of which have the ability to produce damage to the tracheobronchial tissues and lung parenchyma. Retention of inhaled cigarette smoke particles in the respiratory system of man is about 80–90 percent complete with breath holding of two-to-five seconds. Particles penetrate deeply into the respiratory tract and are deposited on the surface of the terminal bronchioles, respiratory bronchioles, and pulmonary parenchyma. Little information is available concerning the specific toxic properties of the particulate phase components. Gas phase components probably have a diffuse though not uniform pattern of distribution. It seems likely on the basis of the physical characteristics of gas absorption and distribution, that a substantial portion is retained along the upper bronchial tract. Certain of the gases known to be present in cigarette smoke are capable of producing pulmonary damage in experimental animals and man.

Cigarette smoke produces significant functional alterations in the upper airways. Like several other agents, cigarette smoke can reduce or abolish ciliary motility in experimental animals. Post-mortem examination of bronchi from smokers shows a decrease in the number of ciliated cells, shortening of the remaining cilia, and changes in goblet cells and mucous glands. The implication of these morphological observations is that functional impairment would result.

Cigarette smoke is also capable of interference with functions in the lower airways. In animal experiments, cigarette smoke appears to affect the physical characteristics of the lung lining layer and to impair alveolar stability. Alveolar phagocytes ingest tobacco smoke components and assist in their removal from the lung. This phagocytic clearance mechanism decompensates under the stress of protracted high-level exposure to cigarette smoke and tobacco smoke components accumulate in the pulmonary parenchyma of experimental animals.

The acute effects of cigarette smoking result in an increase in airway resistance but clinical expression of this change in pulmonary function is not common. The chronic effects of cigarette smoking upon pulmonary function are manifested mainly by a reduction in ventilatory function as measured by the forced expiratory volume.

Histopathological alterations occur as a result of tobacco smoke exposure in the tracheobronchial tree and in the lung parenchyma of man. Changes regularly found in chronic bronchitis—*increase in the number of goblet cells, and hypertrophy and hyperplasia of bronchial mucous glands*—are more often present in the bronchi of smokers than non-smokers. In experimental animals, cigarette smoke consistently produces significant functional altera-