Chapter 10

Non-Neoplastic Respiratory Diseases, Particularly Chronic Bronchitis and Pulmonary Emphysema

Contents

Figure

List of Tables

Chapter 10

This chapter presents the evidence on smoking in relation to the development and progression of the non-neoplastic respiratory diseases. The chronic bronchopulmonary diseases pose a health problem of substantial and steadily growing importance. Bronchitis and emphysema, in particular, severely disable large numbers of men of working age, and have a considerable effect upon mortality as a direct or contributory cause of death. Because of the importance of these diseases to public health, they receive the most attention in this chapter, in accord with the fundamental purpose of the Committee's Report.

The design of this chapter is to consider first the experimental and pathological data, then the clinical and epidemiological data.

ALTERATIONS IN THE RESPIRATORY TRACT AND IN PULMONARY PARENCHYMA INDUCED BY TOBACCO SMOKE

CHARACTERISTICS OF THE EXPOSURE

Composition of Tobacco Smoke

Although the material under this subtitle is dealt with in greater detail in Chapter 6, Chemical and Physical Characteristics of Tobacco and Tobacco Smoke, it is considered here because particle size and other properties of tobacco smoke constituents are of prime importance in the relation between smoking and respiratory diseases.

Tobacco smoke is a heterogeneous mixture of a large number of compounds with gaseous and particulate phases. As it enters the mouth, cigarette smoke is an extremely concentrated aerosol with several hundred million to several hundred billion liquid particles in each cubic centimeter (107, 116, 122). Measurements of the median particle size range from about 0.5 to 1.5 microns; the majority of the measurements have a median closer to 0.5 microns (2). Some of the major classes of compounds which constitute the particulate phase of cigarette smoke and notation of their toxic action on the lung (2) are presented in Table 1 of Chapter 6.

Nine of the gases present in cigarette smoke are considered irritant to the lung (2); Table 2 in Chapter 6 lists some of the known constituents of the gas phase.

Regional Deposition or Retention of Tobacco Smoke

Little is known about the exact composition of cigarette smoke in the respiratory tract after it leaves the mouth. Inhalation of cigarette smoke undoubtedly exposes the airways and pulmonary parenchyma to smoke with

substantially different characteristics from the smoke that first enters the mouth. Insufficient direct evidence is available to characterize this exposure, and existing information is derived largely from substances with analogous physical and chemical features.

The retention or deposition of smoke constituents in the several regions of the respiratory system varies because many factors alter the characteristics of the smoke and probably result in losses as the constituents are drawn deeper into the respiratory system. Included among such factors are the amount and composition of the constituents immediately after burning the tobacco, the method of smoking, the depth of inhalation, and the temperature and humidity of inhaled smoke. The physical laws which govern deposition of particles and absorption of gases and the anatomic structure ultimately determine the pattern of regional retention (2).

When cigarette smoke is inhaled, total retention of particles in the mouth, respiratory tract, and pulmonary parenchyma is about 80-90 percent, even when the smoke is held in the lung for a relatively short period, two-to-five seconds. When deliberately held for periods as long as 30 seconds, retention of particles is almost complete (135).

MOUTH RETENTION OF TOBACCO SMOKE

Removal of tobacco smoke constituents while in the mouth has been studied incompletely. When cigarette smoke is drawn into the mouth and promptly expelled without inhalation, the analyzed weight or fluorescence of the retained tars ranges from 33 percent to 66 percent (18, 71, 135). Experiments utilizing a model of the mouth and airways, but without the deeper portions of the lung, have demonstrated differential regional deposition of certain tar distillation fractions. A cigarette tar fraction distilling at less than 120° C. was deposited in concentrations three times greater in the simulated bronchi than in the mouth; a high-boiling fraction, however, was deposited equally in the mouth and bronchi (57).

The available information suggests that removal of smoke constituents in the mouth may be an important defense mechanism that prevents delivery of certain noxious agents to the tracheobronchial tree and lung parenchyma, but such information is not sufficient to determine which substance may be removed while tobacco smoke components are in the mouth.

RETENTION OF PARTICLES BY THE TRACHEA, BRONCHI, AND PULMONARY TISSUE

Most information pertaining to retention of smoke constituents by the tracheobronchial tree and pulmonary tissue is based on knowledge of physical factors which determine retention of inhaled aerosol particles and on analogies drawn from physiologic studies of aerosol retention in man. In general, the particles of greater size and density are less able to traverse the twisting course of the airways and tend to be removed high in the tracheobronchial tree. Smaller particles penetrate more deeply into the lung and are deposited through gravitational settling or inertial impingement, except for very fine particles which diffuse onto the surface.

The size of virtually all the individual particles in inhaled smoke is probably less than two microns. Data from a number of laboratories indi-

cate that particles smaller than two microns are deposited in the lower respiratory tract during normal breathing under rest conditions. Deep breathing shifts deposition of larger particles into the lower respiratory tract also (2, 83). The lowest proportion of deposition occurs for particles between 0.25-0.50 microns. Diffusion increases for particles below 0.25 microns, and extremely fine particles, approaching molecular size, diffuse so rapidly that many probably remain on the upper bronchial tree. The importance of such minute particles in tobacco smoke, even if present initially, probably is not great since they act as nuclei for vapor condensation and would be expected to grow rapidly (2, 3). Data on sites of intrapulmonary deposition derived from physiological studies indicate that even for particles smaller than two microns, only about five percent are deposited along the bronchial tree.

Radioactive tracers in smoke have been used to study site deposition in animals. Deposition in a diffuse pattern was obtained in dogs inhaling smoke from cigarettes impregnated with K 42, Na 24, and As 76 (192). A similar experiment using 1 131 as the tracer demonstrated substantial bronchial deposition but the physical state of the tracer, whether vapor or particulate, remains uncertain (191). In rabbits, cigarettes impregnated with As 76 produced deposition on the larynx, carina, and major bronchi but this deposition contributed only a small fraction of the total activity retained by the smaller bronchi, bronchioles, and pulmonary tissue (100).

From indirect data, therefore, it is most probable that the vast majority of cigarette smoke particles penetrate deeply into the respiratory tract and are deposited on the surface of the terminal bronchioles, respiratory bronchioles, and pulmonary parenchyma.

RETENTION OF GASES BY THE TRACHEA, BRONCHI, AND PULMONARY PARENCHYMA

Insufficient data are available on the intrapulmonary fate of gases of cigarette smoke to warrant detailed consideration at present. Thorough review of the available information and the known physical characteristics of gas absorption suggest that the speed and depth of inhalation may affect both the amount and site of gas retention; moreover, while the distribution pattern may be diffuse, it seems possible, although not yet demonstrated, that a substantial portion of inhaled tobacco gas and vapor will deposit along the upper bronchial tree (2). In view of the ability of certain of these gases to interfere with normal function of the cleansing mechanisms of the respiratory system (e.g., ciliary motility), such deposition could be of significance in production or augmentation of diseases of the bronchi.

Metabolism and Toxicity of Specific Components in Tobacco Smoke

Little is known about the metabolism of most compounds in tobacco smoke. The fragmentary data have been thoroughly reviewed (2).

Hydrogen cyanide is present in cigarette smoke in concentrations that would be fatal for man were it not for a number of factors which accrue to prevent such a lethal consequence of smoking (2, 60), Among these factors are dilution of the small smoke volume, discontinuous exposure, rapid de-

toxification, and absence of cumulative effect. The cyanide ion is capable of stopping cellular respiration abruptly through inactivation of cytochrome oxidase. In sublethal exposures, the cyanide ion is gradually released from its combination with the ferric ion of cytochrome oxidase, converted to thiocyanate ion (SCN), and excreted in the urine. Thiocyanate blood levels in smokers are three times higher than in non-smokers and differences in relative urinary excretion are even more pronounced (46, 127). It seems quite likely, therefore, that cyanide derived from cigarette smoke is metabolized rapidly in the body, and harmful effects have not been detected.

The principal oxides of nitrogen, nitric oxide and nitrogen dioxide, are present in cigarette smoke in total concentrations varying from 145 to 665 ppm (23). Oxides of nitrogen are partially absorbed in the mouth; absorption after inhalation, however, is almost complete (23, 81). Nitric oxide, one principal oxide of nitrogen in cigarette smoke, is mainly an asphyxiant and is only about one-fifth as toxic as nitrogen dioxide. There is no documented instance of human poisoning due to nitric oxide.

Nitrogen dioxide, however, is a primary lung irritant, presumably as a result of its hydration into nitrous and nitric acids which are subsequently converted to nitrites. Exposure to relatively high concentrations of nitrogen dioxide produces injury sufficient in the human lung to result in pulmonary edema (187). Obliterating fibrosis of the bronchioles has also been observed in man following moderately high exposures (126). In physiologic studies, changes which resemble those of pulmonary obstructive disease have been observed in men who are occupationally exposed to high concentrations of nitrogen oxides (19).

Experimental studies indicate that nitrogen dioxide is capable also of producing pulmonary damage (24, 74, 76). A severe, but reversible, inflammatory reaction in the respiratory bronchioles of rats, rabbits and guinea pigs occurs after a single two-hour exposure to 80-100 ppm. of nitrogen dioxide. Five daily exposures at 15-25 ppm. for two-hour periods produce similar but less severe results (109)

It seems clear from environmental exposures of man to nitrogen dioxide that definite pulmonary damage may result from such exposures. Whether nitrogen dioxide alone, in inhaled cigarette smoke, is capable of producing such damage in man is less certain. Equal amounts of nitric oxide and nitrogen dioxide in cigarette smoke have been reported (81), but recent work indicates that the proportion of nitrogen dioxide is much lower (108). These divergent results and the uncertainty as to the level of nitrogen dioxide exposure necessary to produce pulmonary damage make it very difficult to assess the role of nitrogen dioxide in cigarette smoke.

Formaldehyde gas is present in cigarette smoke in concentrations of 30 ppm. Chronic exposure to 50 ppm. of formaldehyde gas produces an irritant cellular response in mice similar to that produced by tobacco smoke. These changes are found mostly in the trachea; higher levels of exposure are associated with more severe reactions and extension of the involvement to the major but not the smaller bronchi (102).

Exposure of guinea pigs to low concentrations of acrolein, which is also present in cigarette smoke, caused an increase in total respiratory flow resistance accompanied by decreased respiratory rates and increased tidal

volumes (143). It has been found also that acrolein is a potent ciliary depressant (80).

Inhaled vapors of phenol are readily absorbed into the pulmonary circulation and, at 30 to 60 ppm., have produced an organizing pneumonia, the effects being most marked in guinea pigs, less severe in rabbits, and wholly absent in rats (42, 43). Data concerning the metabolism and toxic properties of other constituents of tobacco, such as the polycyclic hydrocarbons, do not suggest that they have a significant role in the development of nonneoplastic respiratory disease in man.

Clearance of Smoke Deposits

Little direct evidence pertaining to clearance mechanisms for smoke deposits is available. There is little reason to believe, however, that smoke deposits are cleared through routes different from the normal self-cleansing mechanism of the lung described in the section on "Pulmonary Hygiene and Ciliary Activity" of this chapter.

Effects of Tobacco Smoke on Defense Mechanisms of the Respiratory System

Pulmonary Hygiene and Ciliary Activity

The cleansing mechanism of the mammalian respiratory system is dependent upon the efficient, integrated functioning of a complex system. From the nose to the terminal bronchioles, a mucous layer in which impacted particles and dissolved materials reside is propelled over the surface and removed from the respiratory tract by the rapid, rhythmic, and purposeful beat of cilia. The mucus is supplied by deep glands in the walls of the airways and by goblet cells. Clearance distal to the terminal bronchioles has become more clearly understood in recent years. Fine particles and gases deposited in the lining of the acinus are removed by several mechanisms. Even relatively insoluble particles dissolve in the lung because of the large surface area-mass ratio of small particles and the high reactivity of body fluids (2). After solution, absorption into the blood stream or lymphatics may result in removal. Remaining particles may undergo phagocytosis or remain free. Some phagocytes enter the alveolar lumen, become laden with foreign material, and are transported to the ciliated air passages to be expelled intact. Some disintegrate along the way and deposit their products on the surface lining. Still other phagocytes may enter interstitial tissues and become sequestrated or be removed to regional lymph nodes. Foreign material which remains free in the fluid lining of the alveolus is transported onto ciliated mucosa by a relatively slow process. The transport results from effects in the fluid lining produced by the mechanics of respiration and replenishment of the alveolar fluid lining.

Inhibition of ciliary motility following exposure to tobacco tars, cigarette smoke, or its constituents has been demonstrated frequently with experimental use of respiratory epithelium from a wide variety of animal species (17, 22, 39, 59, 79, 80, 96, 97, 98, 111, 112, 131, 147, 157, 158, 167, 178).

Similar results have been obtained with ciliated human respiratory epithelium (17, 22). Although all investigations have been conducted *in vitro.* the uniformity of the inhibitory effects in a number of different experimental models is impressive.

Positive ions are present in cigarette smoke. Each cigarette yields about 10^{10} positive ions; negatively charged particles are also present (121). These thermally produced gaseous ions have considerable energy and may produce effects in cells (190). In air free of cigarette smoke, positive ions decrease or abolish ciliary activity. The reduction in ciliary motility which occurs after exposure to cigarette smoke is augmented and sustained by additional exposure to positive ions (112).

Nicotine in high concentrations inhibits ciliary motility although concentrations of nicotine similar to those in tobacco smoke do not affect rabbit, chicken, or human ciliary function (22, 121). In addition, tobacco smoke from low-nicotine cigarettes produced no significant difference in ciliary response from that obtained with cigarettes whore nicotine content had not been altered (121). Hydrogen cyanide, ammonia, acrolein, formaldehyde, nitrogen dioxide, all components of cigarette smoke, possess potent inhibitory activity (40).

There seems to be little doubt that cigarette smoke is capable of producing significant functional alterations of ciliary activity *in vitro.* Such alterations could interfere markedly with the self-cleansing mechanism of the respiratory tract. These *in vitro* results cannot be fully extrapolated to the effects of cigarette smoke on ciliated respiratory tissue of man because of the many variables present in the complex experimental methods, including dosage of the particular agent. Ciliary depressant activity in the environment of man is not limited to the components of tobacco smoke; agents such as ozone and sulfur dioxide, which are important air pollutants but are not found in significant amounts in tobacco smoke, are also potent ciliary depressants.

Morphologic alteration of cilia of smokers has been described (31, 32, 104). The length of cilia in the trachea and bronchial epithelium was measured at autopsy and found to he shorter than in non-smokers. In addition the percentage of cells remaining ciliated is lower in smokers than in non-smokers (9, 10, 104).

Mucus Secretion

Definitive studies on the effect of cigarette smoking upon the quantity and quality of human respiratory tract mucus have not been performed. Alteration in the appearance of mucus after exposure to cigarette smoke has been noted several times. Following exposure to sulfur dioxide, a gas not present in cigarette smoke, changes in the physical properties of mucus have been ohserved (40). Whether such changes result after exposure to gases present in cigarette smoke has not been established. Morphological changes observed in the goblet cells and mucous glands at post-mortem examination, however, support the possibility that mucus production may have been altered during life.

In essence, little has been contributed in this regard since two observation about 100 years ago that a marked increase in mucous secretions in the trachea and larger bronchi of the cat occurred after large doses of nicotine.

Atropinization blocked this effect, indicating that this action of nicotine was mediated by stimulation of the mucous glands since goblet cells are not under nervous control (185). An increase in mucus-secreting cells after exposure of rats to cigarette smoke has also been observed recently (130).

Alveolar Lining

The alveolar surface is covered by a secretion which stabilizes the alveoli and is produced by the alveolar epithelium (79, 151) Little is known of the influence of cigarette smoke on this alveolar lining. The application of cigarette smoke to rat lung extracts, considered to represent the alveolar lining, caused a decrease in surface tension and an increase in surface compressibility. Lung extracts prepared from rats exposed to cigarette smoke during life also showed lower surface tension and increase in surface compressibility. These findings differ markedly from results in non-exposed animals. Such changes during life would he expected to result in a decrease in the efficacy of surface forces stabilizing the alveoli (134). Further interpretation of the results of this single study does not appear warranted; however, because of the great potential significance of the alteration described, further studies should be encouraged.

Phagocytosis

The importance of phagocytosis as a mechanism for clearance of deposits in the acinus has become more clearly established in recent years. The uptake of tobacco tars by phagocytes is well documented in experimental studies. On the basis of solubility, fluorescence, and pigment characteristics of the phagocytized material, and its resemblance to the fluorescence of tobacco smoke condensate, this phagocytized material would appear to contain polycyclic hydrocarbons, The accumulation of exogenous pigmented material in mice has been shown to be directly proportional to both the level and duration of cigarette smoke exposure (119, 121). Similar fluorescent material was observed in rats exposed to cigarette smoke (130) and in the respiratory lining of the white Pekin duck after application of tobacco smoke condensate (166).

Impairment of the efficiency of the phagocytic clearance mechanism after long-term exposure to cigarette smoke apparently occurs in mice (121). Early in the exposure period, the clearance mechanism of the lungs is adequate to the task of aggregating and removing pigmented material and pigment-laden phagocytes; in the final stages of the 2-year experiment, especially at the high dose levels, the phagocytic mechanism appears to be overwhelmed since large areas of parenchyma are flooded with pigment in the absence of phagocytes. A similar suppression of the effectiveness of the phagocytic clearance mechanism for the human lung has been described in pneumoconiosis (41)

Fluorescent histiocytes have been found in the sputum of cigarette smokers but were not detected in the induced sputum of non-smokers (188). The intensity of fluorescence and the number of histiocytes were in direct proportion to the number of cigarettes smoked. These fluorescent histiocytes pre-

sumably represent the phagocytic cells of the acinus which are delivered intact to the sputum.

Phagocytosis appears to serve an important function as a concentrating, localizing, and transport mechanism for redistribution of injurious constituents of cigarette smoke. The full significance of phagocytosis of cigarette smoke constituents in the pathogenesis of disease has not been clarified. Impairment of this function, however, cannot be dismissed since it might be expected to result in lung injury.

Other Mechanisms

Little is known about the role of lymphatics in the removal of tobacco smoke deposits. The evaluation of the effects of smoking on pulmonary function tests will be considered in this Chapter in the section on "Chronic Bronchopulmonary Diseases."

Because the several defense mechanisms of the respiratory system are affected in various ways by tobacco smoke, it may be useful to recapitulate the evidence presented in this section. Substantial experimental evidence indicates that tobacco smoke and certain of its components, like many other substances, can reduce or abolish ciliary motility, at least temporarily, and can slow mucus flow. Impairment of this mechanism in man has not been demonstrated under conditions of cigarette smoking, although it seems logical to assume that alterations would occur. If the removal of noxious agents were slowed, the protracted contact might he expected to result in respiratory tract damage.

Decrease in the number of ciliated cells and shortening of remaining cilia have been described in post-mortem examinations of bronchi from smokers, with implied functional impairment. Alterations in bronchial mucus have been suggested by changes in goblet cells and mucous glands after cigarette-smoke exposure. Increased amount of secretions in the tracheobronchial tree is a frequent observation after exposure to cigarette smoke.

Alteration of the fluid lining of the alveoli in rats as a consequence of cigarette smoke exposure has been reported in the only study of this aspect. The decrease in surface tension and the increase in surface compressibility observed in this study could have great potential significance in terms of human respiratory disease.

That tobacco products are ingested by alveolar phagocytes of the experimental animal and of man seems fairly well documented. Experimental data from animals indicate that the phagocytic mechanism fails under stress of protracted high-level exposure. The potential implications of these observations again appear to loom large for respiratory disease in man but further definition of these effects and quantitation will be necessary before their full significance can be understood.

HISTOPATHOLOGIC ALTERATIONS INDUCED IN THE RESPIRATORY TRACT AND IN PULMONARY PARENCHYMA BY TOBACCO SMOKE

A variety of histopathologic studies from diverse points of view indicate clearly that smoking is associated with abnormal changes in the structure of

both the surface epithelium and wall of the airways, including the mouth. Many of the studies are open to criticism because of inadequate numbers, lack of proper controls, and defects of experimental design, but specific criticisms are different for each study, and the sum of the evidence points unmistakably to the reality of deleterious consequences upon the respiratory tract from tobacco smoke.

Several reports implicate smoking, in particular pipe smoking, as an important etiologic agent in the development of a condition of the *hard palate*, and less often the *soft palate*, known as *stomatitis nicotina* (34, 70, 172, 181). This condition is associated with excessive proliferation of the surface epithelium and overproduction of keratin; the hyperplasia frequently involves the stomas of the salivary glands, leading to blockage and subsequent dilatation of the ducts. Epithelium lining the ducts commonly shows squamous metaplasia. This condition is believed to be very common in pipe smokers but usually disappears upon cessation of smoking.

A somewhat similar morphologic change has been described in the larynx that correlates closely with the cigarette smoking history (45, 170). Epithelial hyperplasia with hyperkeratosis and variable degrees of chronic inflammation and squamous metaplasia are present in the true vocal cords, false cords, and the subglottic area.

The *trachea* and *bronchi* show many morphological changes in the cigarette smoker as compared to the non-smoker (9, 10, 11, 31, 33, 35, 38, 171). Various degrees of hyperplasia, with and without overt atypical change, and metaplasia of the surface epithelium have been described. Deviations from the normal have also been found in the goblet cells, cilia, and mocous glands of smokers. Significant increases in the number of goblet cells and in the degree of mucous distension of the goblet cells were present in whole mounts of bronchial epithelium of smokers (31). Hyperplasia and hypertrophy of mucous glands and a higher proportion of cells with shorter cilia also were observed more frequently in smokers (33, 171). The hypertrophy and hyperplasia of mucous glands from miners correlated much better with the degree of smoking than with exposure to silica (35). Even though the number of non-smokers among the miners was small, the relationship between smoking and mucous gland alteration was very striking.

The studies on goblet cells and mucous glands in smokers and non-smokers are especially important when considered in the light of current concepts of the pathology of *chronic bronchitis.* It is now apparent that one of the commonest morphologic alterations in the bronchi in chronic bronchitis is an increase in goblet cells, and hypertrophy and hyperplasia of the mucons glands (69, 163, 164). Similar findings have been noted in examination of patients with chronic bronchitis in the U.S.A. (182, 183, 184). Although many cases of chronic bronchitis show other morphologic signs of acute and chronic inflammation, these are not as constant as are the glandular changes.

Provided further investigation of the pathologic anatomy of chronic bronchitis in other countries indicates that the disease is essentially identical pathologically, the few British studies on goblet cells, and mucous glands in smokers offer the first anatomic support for the relationship between smoking and chronic bronchitis suggested by several epidemiologic reports. Conceivably, one or more components of cigarette tobacco smoke have the prop-

erty of stimulating mucous cell hypertrophy and hyperplasia in a manner similar to that of other unknown factors which appear to be important in the pathogenesis of chronic bronchitis (cf. 64) This mucous cell activity, accompanied by excessive mucus production, may increase the susceptibility of the tracheobronchial tree to secondary infection with various microorganisms which in turn may lead to acute and chronic inflammation and their consequences. Although this hypothesis (64) has many attractive features, especially in reconciling the epidemiologic and anatomic findings in regard to smoking and chronic bronchitis, it must be emphasized that the anatomic data relating to smoking are still essentially preliminary in nature and require confirmation by more extensive and thorough studies.

Experimental studies on chronic cigarette smoke exposure in animals, although acutely massive compared to human exposures, confirm some of the above morphological findings in man (118, 119, 121). In mice exposed for long periods to cigarette smoke, changes observed in the bronchi and peribronchial tissues were characteristic of severe bronchitis; purulent bronchiolitis severe enough in some instances to cause massive atelectasis, bronchiectasis with organization, and compensatory emphysema were also observed as a response to long-term cigarette smoke exposure. These changes are similar to those described in advanced cases of human bronchitis. In addition to the hypertrophy of mucus-secreting elements already mentioned, scattered areas of purulent bronchiolitis., small abscess cavities, bronchiolar dilatations and alveolar changes also have been observed. The studies in animals therefore support a conclusion that cigarette smoke is irritating to the tracheabronchial tree and is capable of inducing severe acute and chronic bronchitis,

It must be emphasized that the tracheabronchial tree makes only a limited number of histopathologic responses to a large number of different types of injuries. This restriction, perhaps a reflection in part of our methodologic limitations, makes it difficult to identify with any certainty the basic nature of the etiologic agent in any given disease process. It is therefore important to be aware of this element of uncertainty when attempting to compare histopathologic findings in the respiratory system under different environmental conditions and in different species of animals.

Recent studies indicate that changes in the *pulmonary parenchyma* are associated with cigarette smoking (12, 136). Formalin fume-fixed lungs from 83 patients over 40 years of age, from which coal miners were excluded, were examined in a preliminary analysis of a continuing study of the relationship of smoking, parenchymal pigment, and emphysema (136). The causes of death included "diffuse obstructive bronchopulmonary disease." The quantity of "departitioning" (i.e., emphysema) and the amount of black pigment were graded from zero to three. The pigment was not analyzed but was considered to be anthracotic. A close correlation was observed between the quantity of smoking, the quantity of pigment deposited, and the amount of departitioning. At this early phase of the study, the potential etiologic relationships, if any, between the anatomic changes and smoking have not been defined (Figure 1).

Histologic examination of peripheral lung sections has revealed changes in pulmonary parenchyma, the severity of which was proportional to the

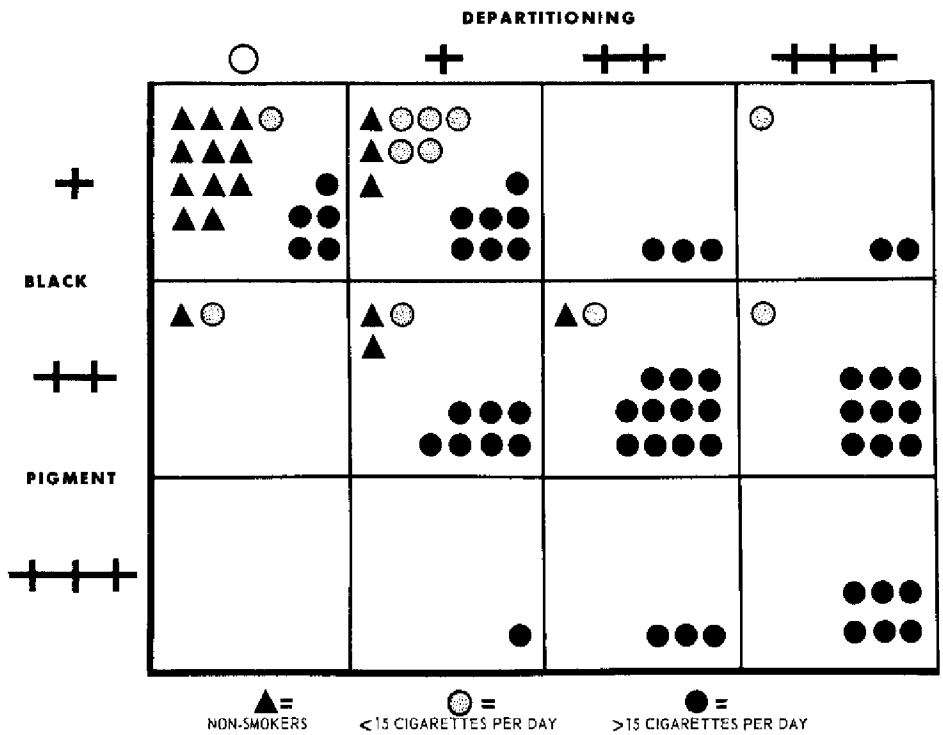

FIGURE 1. Source: Mitchell, R. S. (136)

intensity of cigarette smoking as well as to its duration (12). One section from each of four major lobes of the lung was obtained at autopsy from 1,340 patients for whom a careful smoking history was available. Non-smokers were matched with various categories of smokers by age, race, and occupation and then placed in random order for microscopic examination. The pulmonary ahnormalities, measured by arbitrary gradations, included the following: (a) fibrosis or thickening of alveolar septa, (b) rupture of alveolar septa, (c) thickening of the walls of small arteries and of arterioles, and (d) pad-like attachments to alveolar septa.

The association of increased pulmonary fibrosis and cigarette smoking was apparent in all age groups, (less than 45, 45-49, 60-64, 65-69, 70-74, 75+), even in those who smoked less than one pack per day. The increase in fibrosis was most marked in heavy smokers. Whereas the degree of fibrosis rose slightly with advancing age (60+) in the non-smokers, the rise was far more dramatic in smokers. The findings were similarly dramatic for the degree of rupturing of alveolar septa, the most severe changes being detected in smokers in the older age groups. The same association was found for the degree of thickening of walls of arterioles and small arteries.

Findings in matched pairs of subjects, who differed in respect to one factor but who were alike in respect to another factor, were compared. The degree of pathological change was significantly greater in three categories (pulmonary fibrosis, rupture of alveolar septa, thickening of the walls of small arteries and arterioles) for the following groups:

(1) The older cigarette smoker greater than the younger cigarette smoker;
(2) The one-two pack cigarette smoker greater than “never smoked”:
(3) The one-half pack a day cigarette smoker greater than “never smoked”;
(4) The one-two pack smoker greater than one-half to one pack cigarette smoker;
(5) The current cigarette smoker greater than ex-cigarette smoker who had stopped 20 years.

In addition, the degree of fibrosis (but not the other three indices) was significantly greater:

(1) In one-half to one pack a day cigarette smokers than in less than one-half per day cigarette smokers;
(2) In two pack per day cigarette smokers than one-two pack a day cigarette smokers;
(3) In current cigarette smokers than in ex-cigarette smokers stopped 3-4 years.

Degree of fibrosis. rupturing of alveolar septa, and thickening of walls of the small arteries (but not arterioles) was significantly greater in current cigarette smokers than in ex-cigarette smokers who had stopped 5-19 years. All the changes above were statistically significant at the five percent level.

The degree of fibrosis among men over 60 years of age was studied further by relation to smoking habits in an “age standardized” percentage distribution. Increased fibrosis over that found in non-smokers was striking for current cigarette smokers but some trends in this direction were also noted for current smokers of cigars, of pipes, and of cigars and pipes.

After review of the design of the study with the investigators and the microscopic sections on which judgments were made, some concern remains about two of the four pulmonary abnormalities. Increased thickness of the walls of arteries or arterioles is difficult to interpret on microscopic section, as contraction with decrease in lumen size may simulate an increase in wall thickness. The pad-like attachments are puzzling and the possibility of artifact has been discussed repeatedly. The conclusions drawn from this study are based in large part upon the findings pertaining to fibrosis or thickening of alveolar septa and rupture of alveolar septa.

In summary, histopathologic alterations in the mouth, larynx, tracheobronchial tree and pulmonary parenchyma, associated with smoking, have been documented in man. The alterations in the bronchi support the hypothesis that cigarette smoking is a cause of human chronic bronchitis. Whereas definite pathologic changes in the lung parenchyma of man also are clearly associated with cigarette smoking, the abnormalities observed in the lung parenchyma cannot he related with certainty to recognized disease entities at the present time.

RELATION OF SMOKING TO DISEASES OF THE RESPIRATORY SYSTEM

EFFECTS OF SMOKING ON THE NOSE, MOUTH, AND THROAT

Edema, vascular engorgement, dryness, excess mucus production and epithelial changes have been attributed to cigarette smoking on the basis of clinical observation. Rhinitis, angina, and laryngitis, also observed frequently in cigarette smokers, are reversible on cessation of smoking. Aggravation and prolongation of sinusitis are also attributed to smoking. These observations have become clinical tradition, yet surprisingly little documentation of predictable changes in these tissues as a consequence of smoking is available (129).

Changes in the palatal mucosa ("stomatitis nicotina") and in the laryngeal epithelium (45) closely associated with tobacco smoking have been considered in the earlier discussion of histopathological alterations.

Thus, evidence of progressive non-neoplastic disease in the upper respiratory tract, induced by smoking, is lacking. Only in studies of "stomatitis nicotina" and of epithelial changes in the larynx has there been adequate pathological substantiation of the clinical opinion that alterations are induced by smoking.

SMOKING AND ASTHMA

The definition of asthma of the American Thoracic Society will be used for the purposes of this report (41:

> "Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy.

> "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 he 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) 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, nonrespiratory 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 nonsmokers, 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	Reference	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 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 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-exnected 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

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

Author	Year	Reference	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)	166	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

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

Author	Year	Reference	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	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	Reference	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)	1,292	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	Reference	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
Higgins:						
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.

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

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

Author	Year	Reference	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

[1] Percentages standardized for age.

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 subject 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 measurement 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. Prospectire 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, 119). 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 diffcult 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 pollutants 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-

tions in the upper and lower airways. Such alterations could be expected to interfere with the cleansing mechanisms of the lung.

Pathological changes in pulmonary parenchyma, such as rupture of alveolar septa and fibrosis, have a remarkably close association with past history of cigarette smoking. These changes cannot be related with certainty to emphysema or other recognized diseases at the present time.

Chronic bronchitis and pulmonary emphysema are the chronic bronchopulmonary diseases of greatest health significance. Epidemiological evidence provides the most important information relating cigarette smoking to chronic bronchitis and emphysema. All seven of the major prospective studies show a higher mortality rate for chronic bronchitis and emphysema among cigarette smokers than among non-smokers. In the few studies that have examined mortality rates separately for the two conditions, chronic bronchitis or emphysema, both rates are higher among cigarette smokers than among non-smokers. In one of the studies. the risk of mortality from chronic bronchitis was four times greater among cigarette smokers than among non-smokers. Emphysema was listed as a cause of death 13 times more frequently among smokers in one study. and 7½ times more frequently among smokers in another study.

Extensive prevalence studies, based largely on prevalence of specific symptoms and signs rather than imprecise diagnostic labels, show a consistently more frequent occurrence of cough, sputum, or the two symptoms combined. in cigarette smokers than in non-smokers. These manifestations are the clinical expressions found in chronic bronchitis. The results of the prevalence surveys, however, offer less direct evidence relating cigarette smoking to pulmonary emphysema, as clinical diagnosis of this disease is less exact. Breathlessness, which may result from emphysema or airway obstruction in chronic bronchitis, is associated with cigarette smoking in males, particularly in the older age groups, but not females. Similarly, a consistent association of cigarette smoking and chest illness is more evident for males. In the prevalence surveys in which various combinations of respiratory manifestations have been studied, a greater prevalence of these conditions is found consistently among cigarette smokers.

The majority of clinical studies have noted a relationship between cigarette smoking and chronic bronchitis and emphysema. Cigarette smoking is a more common habit in the United States among patients with chronic bronchitis or emphysema than in the control groups studied. The clinical studies also show a decrease in clinical manifestations of chronic bronchopulmonary disease after cessation of smoking.

Examination of experimental evidence shows that the lung may be damaged by noxious agents found in either tobacco smoke or atmospheric pollotion. In the United States, the noxious agents from cigarette smoking are much more important in the causation of chronic bronchopulmonary disease than are those present as community air pollutants. In the United Kingdom, persons who smoke cigarettes and are exposed frequently to atmospheric pollutants are at greater risk of developing disabling respiratory disease and death than those exposed to either alone.

The relative importance of cigarette smoking also appears to be much greater than occupational exposure as an etiologic factor for the chronic bronchopulmonary diseases.

Cigarette smoking does not appear to cause asthma; in rare instances. allergy to tobacco products has been ascribed a causative role in asthma-like syndromes.

Evidence does not support a direct association between smoking and infectious diseases of the respiratory system. The category, influenza and pneumonia, contributes moderately to the excess mortality of cigarette smokers but other data are not available to extend this observation. The association of cigarette smoking and tuberculosis does not appear to be a direct one, but both are associated with the use of alcohol.

Only for "stomatitis nicotina" and the epithelial changes in the larynx is there sufficient documentation to substantiate the clinical opinion that non-malignant alterations in the month, nose, or throat are induced by smoking, The changes in the mouth are more often associated with pipe smoking but disappear after cessation of smoking.

CONCLUSIONS

1. Cigarette smoking is the most important of the causes of chronic bronchitis in the United States. and increases the risk of dying from chronic bronchitis.

2. A relationship exists between pulmonary emphysema and cigarette smoking hut it has not been established that the relationship is causal. The smoking of cigarettes is associated with an increased risk of dying from pulmonary emphysema.

3. For the bulk of the population of the United States. the importance of cigarette smoking as a cause of chronic bronchopulmonary disease is much greater than that of atmospheric pollution or occupational exposures.

4. Cough, sputum production, or the two combined are consistently more frequent among cigarette smokers than among non-smokers.

5. Cigarette smoking is associated with a reduction in ventilatory function. Among males, cigarette smokers hare a greater prevalence of breathlessness than non-smokers.

6. Cigarette smoking does not appear to cause asthma.

7. Although death certification shows that cigarette smokers have a moderately increased risk of death from influenza and pneumonia, an association of cigarette smoking and infectious diseases is not otherwise substantiated.

REFERENCES

1. Abbott. C. A., Hopkins, W. A., Van Fleit, W. E., Robinson. J. S. A new approach to pulmonary emphysema. Thorax 8: 116-32, 1953.
2. Albert. R. E.. Nelson. N. Special report to the Surgeon General's Advisory Committee on Smoking and Health.

3. Altschuler, B. L. Personal communication to the Surgeon General's Advisory Committee on Smoking and Health.
4. American Thoracic Society. Definitions and classification of chronic bronchitis, asthma and pulmonary emphysema. Amer Rev Resp Dis 85: 762, 1962.
5. Amdur, M. O. The effect of aerosols on the response to irritant gases. In: Davies, C. N. ed. Proceedings of International Symposium on Inhaled Particles and Vapors. Oxford, England, April 1960. London. Pergamon Press, 1961. p. 281-92.
6. Anderson, D. O., Ferris, B. G., Jr. Role of tobacco smoking in the causation of chronic respiratory disease. New Eng J Med 267: 787-94, 1962.
7. Ashford, J. R., Brown, S., Duffield, D. P., Smith, C. S., Fay, J. W. J. The retention between smoking habits and physique, respiratory symptoms, ventilatory function, and radiological pneumoconiosis, amongst coal workers at three Scottish collieries. Brit J Prev Soc Med 15: 106-17, 1961.
8. Attinger, E. O., Goldstein, M. M., Segal, M. S. Effects of smoking upon the mechanics of breathing: I. In normal subjects. II. In patients with cardiopulmonary disease. Amer Rev Tuberc 77: 1-16, 1958.
9. Auerbach, O., Stout, A. P., Hammond, E .C., Garfinkel, L. Bronchial epithelium in former smokers. N Eng J Med 267: 119-25, 1962.
10. Auerbach, O., Stout, A. P., Hammond, E. C., Garfinkel, L. Changes in the bronchial epithelium in relation to cigarette smoking and in relation to lung cancer. New Eng J Med 265: 253-67, 1961.
11. Auerbach, O., Stout. A. P., Hammond, E. C., Garfinkel, L. Changes in bronchial epithelium in relation to sex, age, residence, smoking and pneumonia. New Eng J Med 267: 111-9, 1962.
12. Auerbach, O., Stout, A. P., Hammond, E. C., Garfinkel, L. Smoking habits and age in relation to pulmonary changes: rupture of the alveolar septums, fibrosis and thickening of walls of small arteries and arterioles. New Eng J Med 269: 1045-53, 1963.
13. Badham, C. Observations on the inflammatory affections of the mucous membranes of the bronchiae. London. Callow, 1808.
14. Badham, C. Practical observations on the pneumonic diseases of the poor. Edinburgh Med Surg J 1: 166-70, 1805.
15. Balchum, C. J., Dybicki, J., Meneely, G. R. The dynamics of sulphur dioxide inhalation. AMA Arch Industr Health. (Chicago) 21: 564, 1960.
16. Balchum, O. J., Felton, J. S., Jamison, J. N., Gaines, R. S., Clarke, D. R., Owan, T. A survey for chronic respiratory disease in an industrial city. Amer Rev Resp Dis 86: 675-85, 1962.
17. Ballenger, J. J. Experimental effect of cigarette smoke on human respiratory cilia. New Eng J Med 263: 832-5, 1960.
18. Baumberger, J. P. The amount of smoke produced from tobacco and its absorption in smoking as determined by electrical precipitation. J Pharmacol Exp Ther 21: 47-57, 1927.

19. Bocklake, M. R., Goldman, H. I., Bosman, A. R., Freed, C. C. Long term effects of exposure to nitrous fumes. Amer Rev Tuberc and Pul Dis 76: 398-409, 1957.
20. Bickerman, H. A., Barach, A. L. The effect of cigarette smoking on ventilatory function in patients with bronchial asthma and obstructive pulmonary emphysema. J Lab Clin Med 43: 455-62, 1954.
21. Boake, W. C. A study of illness in a group of Cleveland families. New Eng J Med 259: 1245-9, 1958.
22. Boche, R. D.. Quilligan, J. J. The effects of air pollutants on tissue cultures. Fed Proc Bull 18: 559, 1959.
23. Bokhaven, C., Niessen, H. J. Amounts of oxides of nitrogen and carbon monoxide in cigarette smoke, with and without inhalation. Nature (London) 192: 458-9. 1961.
24. Boren, H. Carbon as a carrier mechanism for irritant gases. Presented at California State Department of Public Health Sixth Air Pollution Medical Research Conference. San Francisco, 1963.
25. Boucot, K. R., Cooper, D. A., Weiss, W. Smoking and health of older men. 1. Smoking and chronic cough. Arch Environ Health (Chicago) 4: 59-78, 1962.
26. Bower, G. Respiratory symptoms and ventilatory function in 172 adults employed in a bank. Amer Rev Resp Dis 83: 684-9 1961.
27. Brinkman. G. L., Coates, E. O., Jr. The prevalence of chronic bronchitis in an industrial population. Amer Rev Resp Dis 86: 47-55, 1962.
28. Bronchitis. Report of a Sub-Committee of the Standing Medical Advisory Committee, Scottish Home and Health Department. Edinburgh, H M Stationery Off, 1963. 59 p.
29. Brown, K. E.. Campbell, A. H. Tobacco, alcohol, and tuberculosis. Brit J Dis Chest 55: 150-8, 1961.
30. Butler, W. T., Alling, D. W., Knight, V. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
31. Chang, S. C. Microscopic properties of whole mounts and sections of human bronchial epithelium of smokers and non-smokers. Cancer 10: 1246-61, 1957.
32. Chang, S. C. Studies of bronchial epithelium from smokers and non-smokers. [Abstract] Proc Amer Ass Cancer Res 2: 99-100, 1956.
33. Chang, C. S. Studies of subepithelial tissue of bronchi from smokers and non-smokers. [Abstract] Proc Amer Ass Cancer Res 2: 286-7, 1958.
34. Chapman, I., Redish, C. H. Tobacco-induced epithelial proliferation in human subject. Long-term effects of pipe smoking on epithelium of hard palate. AMA Arch Path 70: 133-40, 1960.
35. Chatgidakis, C. B. A study of bronchial mucous glands in white South African gold miners. AMA Arch Environ Health 1: 335-42, 1960.
36. Chivers, C. P. Respiratory function and disease among workers in alkaline dusts. Brit J Industr Med 16: 51-60, 1959.
37. College of General Practitioners: Chronic bronchitis in Great Britain: A national survey. Brit Med J 2: 973-9, 1961.

38. Cross, K.R.; Walz, D. V., Palmer, G. K., Warner, E. D. A study of the tracheobronchial epithelium and changes related to smoking. J Iowa Med Soc 51: 137-40, 1961.
39. Dalhamn, T. The effect of cigarette smoke on ciliary activity in the upper respiratory tract. AMA Arch Otolaryng 70: 166-8, 1959.
40. Dalhamn, T., Rhodin, J. Mucous flow and ciliary activity in the trachea of rats exposed to pulmonary irritant gas. Brit J Industr Med 13: 110-3, 1956.
41. Davies, C. M. The handling of particles by the human lung. Brit. Med Bull 19: 49, 1963.
42. Deichmann, W. B., Kitzmiller, M. D., Witherup, S. The effects upon experimental animals of the inhalation of phenol vapor. Amer J Clin Path 14: 273, 1944.
43. Deichmann, W. B., Witherup, S., Dierker, M. Phenol studies 12. J Pharmacol Exp Ther 105: 265, 1952.
44. Densen, P. M., Breuer, J., Bass, H. E., Jones, E. W. New York City Health Department Chronic Respiratory Disease Survey, Interim Report. May 1963.
45. Devine, K. D. Pathologic effects of smoking on the larynx and oral cavity. Proc Mayo Clin 35: 349-52, 1960.
46. Djuric, D., Raicevic, P., Konstantinovic, I. Excretion of thiocyanate in the urine of smokers. Arch Environ Health 5: 12-5, 1962.
47. Dorn, H. F. Personal communication to the Surgeon General's Advisory Committee on Smoking and Health.
48. Dorn, H. F. The increasing mortality from chronic respiratory diseases. Amer Stat Ass Proc Soc Stat Sec p. 148-53, 1961.
49. Dorn, H. F. The mortality of smokers and non-smokers. Amer Stat Ass Proc Soc Stat Sec p. 34-71, 1958.
50. Dowling, H. F., Jackson, G. G., Inouye, T. Transmission of the experimental common cold in volunteers. 2. The effect of certain host factors upon susceptibility. J Lab Clin Med 50: 516-25, 1957.
51. Dysinger, P. W., Lemon, F. R. Pulmonary emphysema in a non-smoking population. Dis Chest 43: 17-25, 1963.
52. Ebert, R. V., Filley, G., Miller, W. F. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
53. Ebert, R. V., Pierce, J. A. Pathogenesis of pulmonary emphysema. Arch Intern Med 111: 34, 1963.
54. Edwards, F., McKeown, T., Whitfield, A. G. W. Association between smoking and disease in men over sixty. Lancet 1: 196, 1959.
55. Edwards, J. H. Contribution of cigarette smoking to respiratory disease. Brit J Prev Soc Med 11: 10-21, 1957.
56. Eich, R. H., Gilbert, R., Auchincloss, J. H., Jr. The acute effect of smoking on the mechanics of respiration in chronic obstructive pulmonary emphysema. Amer Rev Tuberc 76: 22, 1957.
57. Ermala, P., Holsti, L. R. Distribution and absorption of tobacco tars in organs of the respiratory tract. Cancer 8: 673, 1955.
58. Fairbairn, A. S., Fletcher, C. M., Tinker, C. M., Wood, C. H. A comparison of spirometric and peak expiratory flow measurements in men with and without chronic bronchitis. Thorax 17: 168-74, 1962.

59. Falk, H. L., Tremen, H. M., Kotin, P. Effects of cigarette smoke and its constituents on ciliated mucus-secreting epithelium. J Nat Cancer Inst 23: 999-1012, 1959.

60. Fassett, D. W. Cyanides and nitrites. In: Patty, F. A. ed. Industrial hygiene and toxicology; Fassett, D. W. and Irish, D. D. eds. Toxicology. 2 rev ed. New York, Interscience Pub., 1962. Chapter 44, p. 1991-2036.

61. Ferris, B. G., Jr., Anderson, D. O. The prevalence of chronic respiratory disease in a New Hampshire town. Amer Rev Resp Dis 86: 165-77, 1962.

62. Ferris, B. G., Jr., Anderson, D. O., Burgess, W. A. Prevalence of respiratory disease in a flax mill in the United States. Brit J Industr Med 19: 180-5, 1962.

63. Fletcher, C. M. Chronic bronchitis in Great Britain and America. An account of chronic bronchitis in Great Britain with a comparison between British and American experience of the disease. Dis Chest 44: 1-10, 1963.

64. Fletcher, C. M. Chronic bronchitis: Its prevalence, nature and pathogenesis. Amer Rev Resp Dis 80: 483-94, 1959.

65. Fletcher, C. M. Chronic Bronchitis, Smoking and Air Pollution. Tobacco and Health. Charles C. Thomas, Springfield, Illinois, 1962. p. 380-401.

66. Fletcher, C. M., Hugh-Jones, P., McNicol, N. W., Pride, N. B. The diagnosis of pulmonary emphysema in the presence of chronic bronchitis. Quart J Med 32-51, 1963.

67. Fletcher, C. M., Tinker, C. M. Chronic bronchitis; a further study of simple diagnostic methods in a working population. Brit Med J 1: 1491-8, 1961.

68. Flick, A. L., Paton, R. R. Obstructive emphysema in cigarette smokers. AMA Arch Intern Med 104: 518-26, 1959.

69. Florey, H., Carleton, H. M., Wells, A. Q. Mucous secretion in the trachea. Brit J Exp Path 13: 269, 1932.

70. Forsey, R. R., Sullivan, T. J. Stomatitis nicotine. Arch Derm (Chicago) 83: 945-50, 1961.

71. Foster, D., Gassney, H. An investigation of the retention of smoke particulate matter by inhaling and non-inhaling type of cigarette smoker. Presented at the Tobacco Chemists Conference, Hoboken, N.J., Oct. 1958

72. Frank, N. R., Amdur, M. O., Worcester, J., Whittenberger, J. L. Effects of acute controlled exposure to SO_2 on respiratory mechanics in healthy adult males. J Appl Physiol 17: 252-8, 1962.

73. Franklin, W., Lowell, F. C. Unrecognized airway obstruction associated with smoking: A probable forerunner of obstructive pulmonary emphysema. Ann Intern Med 54: 379-86, 1961.

74. Freeman, G., Haydon, G. Effects of continuous low-level exposure to nitrogen dioxide. Presented at California State Department of Public Health Sixth Annual Air Pollution Medical Research Conference. San Francisco, 1963.

75. Fry, J. Chronic bronchitis in general practice. Brit Med J 1: 190-4, 1954.
76. Goldsmith, J. R. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
77. Goldsmith, J. R., Hechter: H. H., Perkins, N. M., Borhani, N. O. Pulmonary function and respiratory findings among longshoremen. Amer Rev Resp Dis 86: 867-74, 1962.
78. Gray, E. LeB. Oxides of nitrogen: Their occurrence toxicity, hazard. AMA Arch Industr Health (Chicago) 19: 479-86, 1959.
79. Gross, P., Hatch, T. Pulmonary clearance: Its mechanism and relation to pulmonary disease. J Occup Med 5: 191-4, 1963.
80. Guillerm, R., Badre, R., Vignon, B. Inhibitory effects of tobacco smoke on the ciliary activity of the respiratory epithelium and nature of the responsible constituents. Bull Acad Nat Med (Paris) 145: 416-23, 1961.
81. Haagen-Smit, A. J., Brunelle, M. F., Hara, J. Nitrogen oxide content of smokes from different types of tobacco. AMA Arch Industr Health (Chicago) 20: 399-400, 1959.
82. Hammond, E. C. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
83. Hatch, T. Respiratory dust retention and elimination. Proc Pneumoconiosis Conf Johannesburg, 1959. p. 133.
84. Hausknecht, R. Experiences of a respiratory disease panel selected from a representative sample of the adult population. Amer Rev Resp Dis 86: 858-66, 1962.
85. Heath, C. W. Differences between smokers and nonsmokers. AMA Arch Intern Med 101: 377-88, 1958.
86. Heimann, H. Effects of air pollution on human health. WHO Monogr Ser No 46: 159-220, 196l.
87. Higgins, I. T. T. An approach to the problem of bronchitis in industry: Studies in agricultural, mining and foundry communities. In: King, E. J., Fletcher, C. M., eds. Symposium on Industrial Pulmonary Diseases. London, Churchill, 1960. p. 195-207.
88. Higgins, I. T. T. Respiratory symptoms, bronchitis, and ventilatory capacity in random sample of an agricultural population. Brit Med J 2: 1198-1203, 1957.
89. Higgins, I. T. T. The role of irritation in chronic bronchitis. In: Orie, N. G. M., Sluiter, H. J. eds. Bronchitis. Springfield, Ill., Thomas, 1961. p. 31-42.
90. Higgins, I. T. T. Tobacco smoking, respiratory symptoms, and ventilatory capacity. Studies in random samples of the population. Brit Med J 1: 325-9, 1959.
91. Higgins, I. T. T., Cochrane, A. L. Chronic respiratory diseases in a random sample of men and women in the Rhondda-Fach in 1958. Brit J Industr Med 18: 93-102, 1961.
92. Higgins, I. T. T., Cochrane, A. L., Gilson, J. C., Wood, C. H. Population studies of chronic respiratory disease: A comparison of miners, foundry workers and others in Staveley, Derbyshire. Brit J. Indnstr Med 16: 255-68, 1959.

93. Higgins, I. T. T., Cochran, J. B. Respiratory symptoms, bronchitis and disability in a random sample of an agricultural community in Dumfriesshire. Tubercle 39: 296-301, 1958.
94. Higgins, I. T. T., Oldham, P. D. Ventilatory capacity in miners. A five year follow-up study. Brit J Industr Med 19: 65-76, 1962.
95. Higgins, I. T. T., Oldham, P. D., Cochrane, A. L., Gilson, J. C. Respiratory symptoms and pulmonary disability in an industrial town. Survey of a random sample of the population. Brit Med J 2: 904-9, 1956.
96. Hilding, A. C. On cigarette smoking, bronchial carcinoma and ciliary action. 2. Experimental study on the filtering action of cow's lung, the deposition of tar in the bronchial tree and removal by ciliary action. New Eng J Med 254: 1154-60, 1956.
97. Hilding, A. C. On cigarette smoking, bronchial carcinoma and ciliary action. 3. Accumulation of cigarette tar upon artificially produced deciliated islands in the respiratory epithelium. Ann Otol 65: 116-30, 1956.
98. Hill, L. The ciliary movement of the trachea studied in vitro. Lancet 2: 802-5, 1928.
99. Hogner, R. Tobacco poisoning without using tobacco. Amer Med 26: 111-2, 1920.
100. Holland, R. H., Wilson, R. H., Morris, D., McCall, M. S.. Lanz, H. The effect of cigarette smoke on the respiratory system of the rabbit. Cancer 11: 709-12, 1958.
101. Holland, W. W. A respiratory disease study of industrial groups. Arch Environ Health (Chicago) 6: 15-22, 1963.
102. Horton, A. W., Tye, R., Stemmer, K. L. Experimental carcinogenesis of the lung. Inhalation of gaseous formaldehyde or an aerosol of coal tar by C3H mice. J Nat Cancer Inst 30: 31-43, 1963.
103. Hyatt, R. E., Kistin, A. D., Mahaw, T. K. Respiratory disease in southern West Virginia coal workers. Amer Rev Resp Dis (In Press).
104. Ide, G., Suntzeff, V., Cowdry, E. V. A comparison of the histopathology of the tracheal and bronchial epithelium of smokers and non-smokers. Cancer 12: 473-84, 1959.
105. Jimenez-Diaz, C., Sanchez Cuenca, B. Asthma produced by susceptibility to unusual allergies. Linseed, insects, tobacco, and chicory. J Allerg 6: 397-403. 1935.
106. Joules, H. A preventive approach to common diseases of the lung. Brit Med J 2: 1259-63. 1954.
107. Keith, C. H., Newsome, J. R. Quantitative studies on cigarette smoke. 1. An automatic smoking machine. Tobacco 144: (13) 26-32. Mar 29, 1957.
108. Kensler, C. J., Battista, S. P. Components of cigarette smoke with ciliary-depressant activity. Their selective removal by filters containing activated charcoal granules. New Eng J Med 269: 1161-66, 1963.

109. Kleinerman, J., Wright, G. W. The reparative capacity of animal lungs after exposure to various single and multiple doses of nitrite. Amer Rev Resp Dis 83: 423-24. 1961.
110. Kler, J. H. An analysis of colds in industry. Tr Amer Acad Opthal Otol 49: 201-7, 1945.
111. Kordik, P., Bulbring, E., Bum, J. H. Ciliary movement and acetylcholine. Brit J Pharmacol 7: 67-79, 1952.
112. Krueger, A. P., Smith, R. F. Effects of gaseous ions on tracheal ciliary rate. Proc Soc Exp Biol Med 98: 412-4, 1958.
113. LaBelle, C. W., Long, J. E., Christofano, E. E. Synergistic effects of aerosols. Particulates as carriers of toxic vapors. Arch Industr Health (Chicago) 11: 297-304, 1955.
114. Laennec, R. T. H. A treatise on the disease of the chest. Translated by J. Forbes. Published under the auspices of the Library of the New York Academy of Medicine by Hafner, NY 81-97, 1962.
115. Landau, E., Morton, J. An epidemiologic view of chronic pulmonary insufficiency in the United States. Amer Rev Resp Dis 83: 405-7, 1961.
116. Lager, G., Fisher, M. A. Concentration and particle size of cigarette-smoke particles. AMA Arch Industr Health (Chicago) 13: 372-8, 1956.
117. Leese, W. L. B. An investigation into bronchitis. Lancet 2: 762-5, 1956.
118. Leuchtenberger, C., Leuchtenberger, R., Doolin, P. F. A correlated histological, cytological and cytochemical study of the tracheabronchial tree and lungs of mice exposed to cigarette smoke. Cancer 11: 490-506, 1958.
119. Leuchtenberger, C., Leuchtenberger, R., Zebrun, W., Shaffer, P. A correlated histological, cytological, and cytochemical study of the tracheabronchial tree and lungs of mice exposed to cigarette smoke. 2. Varying responses of major bronchi. Cancer 13: 721-32, 1960.
120. Liebeschuetz, H. J. Respiratory signs and symptoms in young soldiers and their relationship to smoking. J Roy Army Med Corps 105: 76-81, 1959.
121. Liggett & Myers Tobacco Co., Arthur D. Little, Inc. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
122. Lindsey, A. J. Some observations on the chemistry of tobacco smoke. In: James, G., Rosenthal, T., eds. Tobacco and Health. Springfield, Ill., Thomas, 1962. p. 21.
123. Loudon, R. G. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
124. Lowe, C. R. An association between smoking and respiratory tuberculosis. Brit Med J 2: 1081-6, 1956.
125. Lowell, F. C., Franklin, W., Michelson, A. L., Schiller, I. W. Chronic obstructive pulmonary emphysema: A disease of smokers. Ann Intern Med 45: 268-74, 1956.
126. Lowry, T., Schuman, L. M. Silo-filler's disease-a syndrome caused by nitrogen dioxide. JAMA 162: 153-60, 1956.

127. Maliszewski, T. F., Bass D. E. True and apparent thiocyanate in body fluids of smokers and nonsmokers. J Appl Physio1 8: 289-91, 1955.
128. Manos, N. E., Cooper, W. C. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
129. McFarland, J. J., Webb, B. M. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
130. Mellors, R. C. Microscopic localization of tobacco smoke products in the respiratory tracts of animals exposed to cigarette smoke. [Abstract] Proc Amer Ass Cancer Res 2: 325, 1958.
131. Mendenhall, W. L., Shreeve, K. Effect of tobacco smoke on ciliary action. J Pharmacol Exp Ther 69: 295, 1940. The effect of cigarette smoke on the tracheal cilia. Ibid. 60: 111-2, 1937.
132. Merrill, M. H. Public health responsibilities and program possibilities in chronic respiratory diseases. Amer J Public Health 53: (3) (supp). 25-33, 1963.
133. Mills, C. A. Tobacco smoking: Some hints of its biologic hazards. Ohio Med J 46: 1165-70; 1950.
134. Miller, D., Bondurant, S. Effects of cigarette smoke in the surface characteristics of lung extracts. Amer Rev Resp Dis 85: 692-6, 1962.
134a. Miller, J. M. Special Report to the Surgeon General's Advisory Committee on Smoking and Health.
135. Mitchell, R. I. Controlled measurement of smoke-particle retention in the respiratory tract. Amer Rev Resp Dis 85: 526-33, 1962.
136. Mitchell, R. S. Personal communication to the Surgeon General's Advisory Committee on Smoking and Health.
137. Mitchell, R. S., Filley, G. F. Personal communication to the Surgeon General's Advisory Committee on Smoking and Health.
138. Mitchell, R. S., Toll, G., Filley, G. The early lesions in pulmonary emphysema. Amer J Med Sci 243: 409-18, 1962.
139. Mark, T. A comparative study of respiratory diseases in England and Wales and Norway. Norwegian Universities Press, 1962. Also: ACTA Med Scand 172 (Supp 384) : l-100, 1962.
140. Morris, J. N. Uses of epidemiology. Edinburgh, Livingstone, 1957. 135 p.
141. Moriyama, I. M. Chronic respiratory disease mortality in the United States. Public Health Rep 78: 743-8, 1963.
142. Motley. H. L., Kuzman, W. J. Cigarette smoke. Its effect on pulmonary function measurements. Calif Med 88: 211-21, 1958.
143. Murphy, S. D., Klingshirn, D. A., Ulrich, C. E. Respiratory response of guinea pigs during acrolein inhalation and its modification by drugs. J Pharmacol Exp Ther 141: 79-83, 1963.
144. Murphy, S. D., Leng. J. K., Ulrich, C. E., Davis. H. V. Effects on experimental animals on brief exposure to diluted automobile exhaust. Presented at Air Pollution Research Conference, December 9, 1961. California.
146. Nadel, J. A., Comroe, J. H. Acute effects of inhalation of cigarette smoke on airway conductance. J Appl Physiol 16: 713-6, 1961.

147. Nakashima, T. Pharmacological studies on ciliary movement. Nagasaki Igasakkai Zassi 14: 2219-37, 1936. [Abstract in English] Jap J Med Sci, Sect pharmacol 11: 42, 1938.
148. Olsen, H. C., Gilson, J. C. Respiratory symptoms, bronchitis and ventilatory capacity in men. An Anglo-Danish comparison, with special reference to differences in smoking habits. Brit Med J 1: 450-6, 1960.
149. Oswald, N. C., Harold, J. T., Martin, W. J. Clinical pattern of chronic bronchitis. Lancet 2: 539-43, 1953.
150. Oswald, N. C., Medvei, V. C. Chronic bronchitis; the effect of cigarette smoking. Lancet 2: 843-47, 1955.
151. Pattle, R. E. Properties function, and origin of the alveolar lining layer. Proc Royal Soc Biol 148: 217-40, 1958.
152. Pattle R. E., Burgess, F. Toxic effects of mixtures of sulfur dioxide and smoke with air. J Path Bact 73: 411-9, 1957.
153. Payne, M., Kjelsberg, M. Respiratory symptoms, lung function and smoking habits in a total community--Tecumseh, Michigan. Paper presented before the Epidemiology Section of the American Public Health Association in Miami Beach, October 17, 1962.
154. Pemberton, J., Goldberg, C. Air pollution and bronchitis Brit Med J 2: 567-70, 1954.
155. Phelps, H. W., Koike, S. Tokyo-Yokohama asthma. Amer Rev Resp Dis 86: 55-63, 1962.
156. Phillips, A. M., Phillips, R. W., Thompson, J. L. Chronic cough: analysis of etiologic factors in a survey of 1,274 men. Ann Intern Med 45: 216-31, 1956.
157. Proetz A. Some preliminary experiments in the study of cigarette smoke and its effect upon the respiratory tract. Ann Otol 48: 176-94. 1939.
158. Rakieten. N., Rakieten, M. L., Feldman, D., Boykin, M. J., Jr. Mammalian ciliated respiratory epithelium. Studies with particular reference to the effects of menthol. nicotine. and smoke of mentholated and nonmentholated cigarettes. Arch Otolaryng (Chicago) 56: 494-503, 1942.
159. Read, J., Selby, T. Tobacco smoking and ventilatory function of the lungs. Brit Med J 2: 1104-8, 1961.
160. Reid, D., Fairbairn, A. S. Air pollution and other local factors in respiratory disease. Brit J Prev Soc Med 12: 94-103, 1958.
161. Reid, D. D. General epidemiology of chronic bronchitis. Proc Roy Soc Med 49: 767-71, 1956.
162. Reid, L. Chronic bronchitis and hypersecretion of mucus. Lect Sci Basis Med 8: 235-8, 1958-59.
163. Reid, L. Measurement of the bronchial mucous gland layer: A diagnostic yardstick in chronic bronchitis. Thorax 15: 132-41, 1960.
164. Reid, L. M. Pathology of chronic bronchitis. Lancet 1: 275-8, 1954.
165. Revotskie, N., Kannell, W., Goldsmith, J. R., Dawber, T. R. Pulmonary function in a community sample. Amer Rev Resp Dis 86: 907-11, 1962.

166. Rigdon, R. H. Effect of tobacco condensate on the respiratory tract of the white Pekin duck. AMA Arch Path (Chicago) 69: 55-63, 1960.
167. Rivera, J. A. Cilia, ciliated epithelium and ciliary activity. Int Ser Monogr Pure Appl Biol 15: 1-167, 1962.
168. Rosen, F. L. Bronchial asthma in the young male adult. Ann Allerg 4: 247-60, 1946.
169. Rosen, F. L., Levy, A. Bronchial asthma due to allergy to tobacco smoke in an infant. A case report. JAMA 144: 620-1, 1950.
170. Ryan, R. F., McDonald, J. R., Devine, K. D. The pathologic effects of smoking on the larynx. AMA Arch Path (Chicago) 60: 472-80, 1955.
171. Sanderud, K. Squamous metaplasia of the respiratory tract epithelium. 2. Relation to tobacco smoking, occupation and residence. Acta Path Microbial Scand 43: 47-61, 1958.
172. Saunders, W. H. Nicotina stomatitis of the palate. Ann Otol 67: 618-27, 1958.
173. Schoettlin, C. E. The health effect of air pollution on elderly males. Amer Rev Resp Dis 86: 878-97, 1962.
175. Shah, J. R., Warawadekar, M. S., Deshumkh, P. A., Phutene, P. N. Institutional survey of pulmonary tuberculosis with special reference to smoking habits. Indian J Med Sci 13: 381-92, 1959.
176. Short, J. J., Johnson, H. J., Ley, H. A., Jr. The effects of tobacco smoking on health. A study of 2,031 medical records. J Lab Clin Med 24: 586-9, 1939.
177. Simonsson, B. Effect of cigarette smoking on the forced expiratory flow rate. Amer Rev Resp Dis 85: 534-9, 1962.
178. Sollmann, T., Gilbert, A. J. Microscopic observations of bronchiolar reactions. J Pharmacol Exp Ther 61: 272-85, 1962.
179. Stokinger, H. E., Wagner, W. D., Dobrogorski, O. J. Ozone toxicity studies. 3. Chronic injury to lungs of animals following exposure. at low levels. AMA Arch Industr Health 16: 514-22, 1957.
180. Sweet, H. C., Wyatt, J. P., Fritsch, A. J., Kinsella, P. W. Panlobular and centrilobular emphysema: Correlation of clinical findings with pathologic patterns. Ann Intern Med 55: 565-81, 1961.
181. Thoma, K. H. Stomatitis nicotina and its effects on the palate. Amer J Orthodont 27: 38-47, 1941.
182. Thurlbeck, W. M. A clinico-pathological study of emphysema in an American hospital. Thorax 18: 59-67, 1963.
183. Thurlbeck, W. M., Angus, G. E. The relationship between emphysema and chronic bronchitis as assessed morphologically. Amer Rev Resp Dis 87: 815-9, 1963.
184. Thurlbeck, W. M., Angus, G. E., Pare, J. A. P. Mucous gland hypertrophy in chronic bronchitis, and its occurrence in smokers. Brit J Dis Chest 57: 73-78, 1963.
185. Truhart, H. Ein beitrag zur nicotinwirkung. Dorpat, 1869. Thesis, 70 p.
186. U.S. Department of Health, Education, and Welfare. Disability applicants under the old-age survivors and disability program. 1960 selected data, January 1962.

187. Von Oettingen, W. F. Toxicity and potential dangers of nitrous fumes. Public Health Bull 272: l-34, 1941.
188. Vassar, P. S., Culling, C., Saunders, A. M. Flourescent histiocytes in sputum related to smoking. AMA Arch Path (Chicago) 70: 649-52, 1960.
189. Walker, I. C. The treatment of patients with bronchial asthma with subcutaneous injections of proteins to which they are sensitive. J Med Res 36: 423-80, 1917.
190. Westermark, T. Gaseous ions and their possible role in the etiology of lung cancer and some observations on free charges in cigarette smoke. Acta Med Scand 170: (Suppl 369) 119-20, 1961.
191. Wolff, W. A., Tuttle, J. G., Godfrey, J. M. Radioautographic method for studying deposition of cigarette smoke in the dog lung. Abstract Fed Proc 13: 324, 1954.
192. Wolff, W. A., Purdom, E. G., Isenhower, J. A. The use of radio-isotopes as tracers in cigarette smoke. N Carolina Med J 15: 159-63, 1954.
193. Wright, G. W., Lloyd, T. The pulmonary reaction of normal and emphysematous persons to inhalation of SO_2, fly ash, and moisture. 3d Air Pollution Research Seminar, U.S. Public Health Service.
194. Zamel, N., Youssef, H. H., Prime, F. J. Airway resistance and peak expiratory flow-rate in smokers and non-smokers. New Orleans, 1960. Lancet 1: 1237-8, 1963.