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Chapter 10

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

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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 I 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 whose 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 be 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 observed (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 the 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 be 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 be 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 mucous 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 mucous 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 tracheobronchial tree and is capable of inducing severe acute and chronic bronchitis.

It must be emphasized that the tracheobronchial 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

BLACK PIGMENT AND EMPHYSEMA IN LUNGS OF 83 PATIENTS

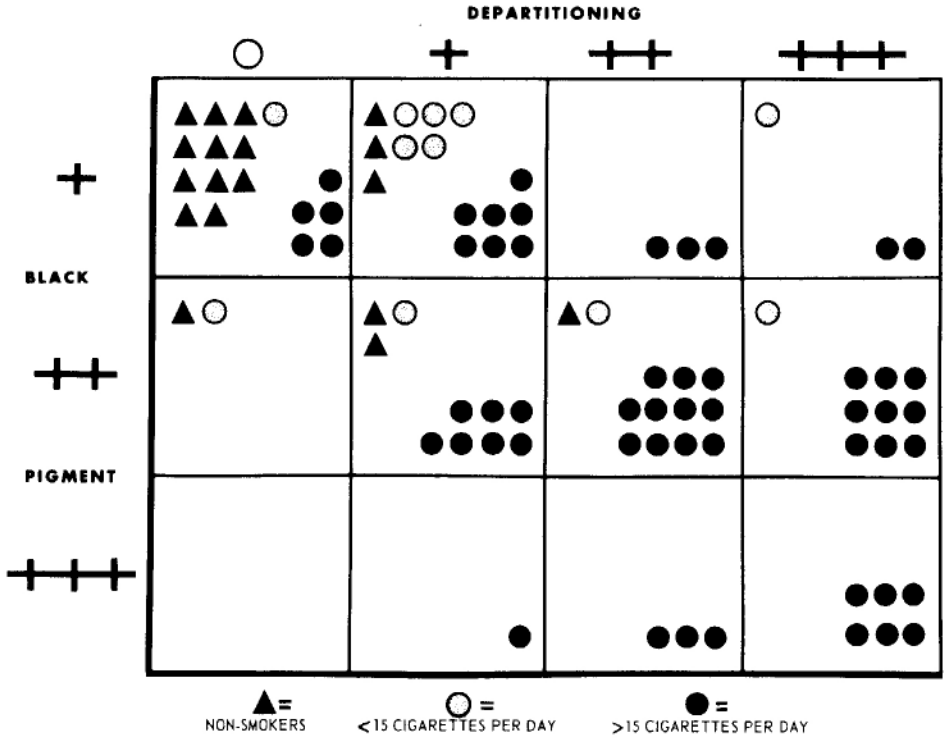

FIGURE 1. Source: Mitchell, R. S. (136)

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 abnormalities, 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 be 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 (4):

> "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.