cluded: "... vasoconstriction, decrease in blood flow rate and frequency of plasma spacing, blocking of blood flow in varying numbers of nutritive capillaries, shunting of blood from arterioles to venules...." These microcirculatory changes were said to result in a decrease of nutritive blood flow in tissue.

As mentioned in the discussion of CHD, Kjeldsen (*31, 32*) studied several smoking patients with occlusive peripheral vascular disease whose COHb levels were significantly higher than those of control smokers. The levels of COHb in many of these patients were comparable to those associated with experimental atherosclerosis in animals. Astrup, et al. (*4*) have suggested that prospective studies should be performed to investigate the relationship between COHb levels and the incidence of arterial disease.

In the Prague study (*19*) intermittent claudication was significantly ($P < .01$) more common among cigarette smokers than nonsmokers. Twenty percent of the men in the age group of 60 to 64 who were heavy smokers (more than 25 cigarettes a day) had intermittent claudication.

Räf (*44*) reported that all but 4 of the 98 patients admitted for peripheral vascular surgery at the Karoline Hospital, Sweden, were smokers.

Mathiesen, et al. (*38*) in Denmark followed the spontaneous course of arterial insufficiency in 211 patients. Cessation of smoking increased the number of patients displaying spontaneous improvement.

ORAL CONTRACEPTIVES, THROMBOPHLEBITIS, AND SMOKING

In two studies from Great Britain and one from the United States, it was reported that the use of oral contraceptives was associated with a significantly increased risk of developing venous thromboembolism (*46, 58, 59*). The British investigators also noted in their initial report that the affected patients were, on the average, heavier smokers than controls (*58*). However, after an additional year of study, a similar effect was not noted and they concluded (*59*): "... the earlier difference between the smoking habits of the two groups can thus reasonably be attributed to chance ($P = 0.08$)." The American investigator (*45*) found "... no evidence that smoking, acting either independently or in conjunction with oral contraceptives, is a factor in idiopathic thromboembolism."

Cigarette smoking has not been clearly demonstrated to be a factor that contributes to the risk of idiopathic thromboembolism associated with the use of oral contraceptives. Nevertheless, the possibility that it may act to increase that risk has not yet been completely ruled out.

HIGHLIGHTS OF CURRENT CARDIOVASCULAR INFORMATION

In addition to the comprehensive summary from the 1971 report, "The Health Consequences of Smoking" (*56*), cited earlier in this chapter, the following statements are made to emphasize the most recent developments in the field:

1. Recent epidemiological studies from several countries confirm that cigarette smoking is one of the major risk factors contributing to the development of CHD. Avoidance of cigarette smoking is of importance in the primary prevention of CHD.
2. Studies in man and animals have shown a greater myocardial arteriole wall thickness in smokers than nonsmokers.
3. Experimental and epidemiological investigations implicate the elevation of carboxyhemoglobin levels in smokers as a contributor to the development of CHD and arteriosclerotic peripheral vascular disease.
4. Cigarette smoking is considered to be the major cause of pulmonary heart disease (cor pulmonale) in the United States in that it is the most important cause of chronic nonneoplastic bronchopulmonary diseases. Avoidance of cigarette smoking is of importance in the primary prevention of pulmonary heart disease.

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CHAPTER 3

Non-neoplastic Bronchopulmonary Diseases

Contents

INTRODUCTION

Chronic bronchitis and emphysema are the chronic bronchopulmonary diseases of greatest health importance in the United States (*71*). The 1971 report, "The Health Consequences of Smoking" (*70*), summarized the relationship between smoking and these diseases as follows:

1. Cigarette smoking is the most important cause of chronic obstructive bronchopulmonary disease in the United States. Cigarette smoking increases the risk of dying from pulmonary emphysema and chronic bronchitis. Cigarette smokers show an increased prevalence of respiratory symptoms, including cough, sputum production, and breathlessness, when compared with nonsmokers. Ventilatory function is decreased in smokers when compared with nonsmokers.

2. Cigarette smoking does not appear to be related to death from bronchial asthma although it may increase the frequency and severity of asthmatic attacks in patients already suffering from this disease.

3. The risk of developing or dying from COPD among pipe and/or cigar smokers is probably higher than that among nonsmokers while clearly less than that among cigarette smokers.

4. Ex-cigarette smokers have lower death rates from COPD than do continuing smokers. The cessation of cigarette smoking is associated with improvement in ventilatory function and with a decrease in pulmonary symptom prevalence.

5. Young, relatively asymptomatic, cigarette smokers show measurably altered ventilatory function when compared with nonsmokers of the same age.

6. For the bulk of the population of the United States, the importance of cigarette smoking as a cause of COPD is much greater than that of atmospheric pollution or occupational exposure. However, exposure to excessive atmospheric pollution or dusty occupational materials, and cigarette smoking may act jointly to produce greater COPD morbidity and mortality.

7. The results of experiments in both animals and humans have demonstrated that the inhalation of cigarette smoke is associated with acute and chronic changes in ventilatory function and pulmonary histology. Cigarette smoking has been shown to alter the mechanism of pulmonary clearance and adversely affect ciliary function.
8. Pathological studies have shown that cigarette smokers who die of diseases other than COPD have histologic changes characteristic of COPD in the bronchial tree and pulmonary parenchyma more frequently than do nonsmokers.
9. Respiratory infections are more prevalent and severe among cigarette smokers, particularly heavy smokers, than among nonsmokers.
10. Cigarette smokers appear to develop postoperative pulmonary complications more frequently than nonsmokers.

Recent epidemiological, autopsy, and experimental studies confirm and extend the foregoing statements.

EPIDEMIOLOGICAL STUDIES

COPD Mortality

Over a period of 4 to 8 years, Burrows and Earle (*10*) studied 200 patients with symptomatic COPD whose mean FEV_1 was 1.0 $\pm$ 0.4 liter. Ninety-seven percent of these patients had a history of cigarette smoking; the average consumption for the entire group of 200 individuals was 23 cigarettes a day over a period of 41 years. Upon entry into the study, 59 percent were still regular smokers and 38 percent had discontinued smoking. Eighty-nine percent of the group were males and the mean age was 59.1 years.

A 47 percent 5-year mortality was observed in these 200 patients, and most deaths were "... directly attributable to the underlying lung disease or one of its complications." The relationship of continued smoking to the course of the disease was difficult to interpret. Patients who stopped smoking prior to entry into the study had a poorer survival than those who continued to use cigarettes. This was related to a tendency for patients to give up smoking when their illness was severe, and "... the apparent advantage of smokers was eliminated when patients with similar FEV_1 levels were compared." The authors reported no reduction of mortality in the group of patients who stopped smoking, even when smokers and ex-smokers with similar FEV_1 levels were compared.

Reduction of cigarette smoking was associated with a history of reduced expectoration, smaller measured sputum volume, and "... a favorable course of the vital capacity ($P < .01$)...."

The 1971 report, "The Health Consequences of Smoking" (*70*), included an analysis of the variety of ways in which smoking may be related to disease. COPD was cited as an example in which smoking probably initiates a disease process by producing progressive, irreversible damage. The 200 patients reported by Burrows and Earle (*10, 11*) may be representative of patients who have experienced progressive and irreversible pulmonary damage after many years of exposure to cigarette smoke. In such cases, "... cessation of smoking leaves impaired function which does not improve appreciably but does not continue to deteriorate from continued exposure to cigarette smoke. However, such function may deteriorate through aging or through exposure to other harmful agents" (*70*).

COPD Morbidity

New reports of chronic bronchopulmonary disease prevalence support the findings of earlier studies in which a greater prevalence was found among smokers than nonsmokers.

A repeat study of a Berlin, New Hampshire, population sample, which included more than 1,500 individuals, was carried out in 1967 by Ferris, et al. (*27*). In both this survey and the earlier 1961 survey, a greater prevalence of chronic nonspecific respiratory disease was found in cigarette smokers than nonsmokers.

The 1967 Berlin study demonstrated that cigarette smokers who inhaled deeply or moderately had generally higher prevalences of chronic nonspecific respiratory disease than those who did not inhale or inhaled only slightly.

After standardization for age, sex, and smoking habits, the prevalence of chronic nonspecific respiratory disease in the 1967 survey sample was slightly lower than in 1961. This may be accounted for by a decrease in air pollution.

In a random sample of 609 residents of Glenwood Springs, Colorado, a high prevalence of chronic bronchitis was found to be strongly related to smoking, particularly of cigarettes, and this relationship was independent of age, sex, or history of dust exposure at work (*52*). Chronic airway obstruction was found to be predominantly a disease of elderly male smokers and increased in frequency with increasing age after 49 years.

The Tecumseh study is a well-known continuing epidemiologic investigation of the entire community of Tecumseh, Michigan. In this study the relationship of parental longevity to ventilatory function and prevalence of chronic nonspecific respiratory disease

among sons was recently analyzed (*17*). Death before age 65 of either parent was related to low values of 1-second forced expiratory volume among the sons. Maternal death before age 65 was also associated with increased prevalence of chronic bronchitis and emphysema among sons. Some, but not all, of these relationships were accounted for by differences in smoking habits of the sons. The authors also concluded: "The evidence strongly suggests that constitutional factors are involved" (*17*).

A higher prevalence of chronic bronchitis was found among smokers than nonsmokers ($P < .01$) in a study of 710 Yugoslavian workers (*43*). There was a direct relationship between the lifetime number of cigarettes smoked and the presence of chronic bronchitis.

Several papers have been published recently comparing respiratory symptoms such as cough and sputum production among smokers and nonsmokers in different populations. Two of the new studies were prospective investigations (*15, 38*). In all instances, symptoms were more common among cigarette smokers than nonsmokers (*1, 6, 8, 15, 38, 52, 63, 75*). In the three studies which reported on pipe and cigar smokers, the frequency of respiratory symptoms in this group was, in general, intermediate between those of cigarette smokers and nonsmokers (*6, 15, 52*).

Results of studies of pulmonary function in representative samples of different populations (*6, 17, 38, 63*), surveys of employees (*15, 43, 57*), and normal volunteers (*75*) indicate that cigarette smokers have lower average pulmonary function than nonsmokers.

Pulmonary diffusing capacity was found by Van Ganse, et al. (*72*) to decrease in men and women with aging and with an increase in current or lifetime cigarette consumption.

In general, a dose-response relationship between cigarette consumption and the development of respiratory symptoms and/or impaired pulmonary function was found in both men and women; as cigarette consumption increased, these abnormalities were found more frequently (*6, 38, 52, 72, 75*).

Woolf and Suero (*75*) studied the respiratory effects of cigarette smoking in 298 normal women. The prevalence of cough, sputum production, wheezing, and shortness of breath increased progressively with increased cigarette smoking. The results of the following tests of pulmonary function were significantly lower in smokers than in nonsmokers: forced vital capacity, forced expiratory volume in one second, maximal mid-expiratory flow, arterialized capillary blood oxygen tension at rest, specific conductance, and pulmonary diffusing capacity and fractional uptake of carbon monoxide during exercise.

Seely, et al. (*63*) examined 365 high school students in the New Haven area. They found that students with 1 to 5 years' smoking experience had excessive cough, sputum production, and shortness of

breath. These young smokers also had lower flow rates at mid-vital capacity and at lower lung volumes than nonsmoking students. The authors have raised the question of whether smoking by high school students may lead to developmental arrest of the lung. They feel that follow-up pulmonary function studies in adolescents who stop smoking will help clarify this question.

In a study of 556 high school students from Oklahoma City, Addington, et al. (*1*) reported that respiratory symptoms were significantly more frequent in smokers than nonsmokers, but no significant differences were noted in the FEV_1 and the mean vital capacity.

Snider, et al. (*65*) investigated 1,403 patients with documented pulmonary tuberculosis for the presence of obstructive pulmonary disease. Airway obstruction was found in 62 percent of white men, 37 percent of nonwhite men, 36 percent of white women, and 17 percent of nonwhite women. Sixty-eight percent of the patients were current smokers and 15 percent were ex-smokers. Heavy smoking had less effect on the presence of airway obstruction than advanced tuberculosis or older age. These data were interpreted as showing the predominant importance of tuberculosis as a factor leading to airway obstruction in tuberculous patients. However, the authors also concluded: "The present data suggest the possibility of an additive effect of smoking with tuberculosis in producing airway obstruction."

Cessation of Smoking

The salutary effect of stopping cigarette smoking on COPD mortality and morbidity has been noted in previous reports of the Surgeon General (*69, 70*).

A recent statement from the "Pulmonary Heart Disease Study Group" of the Inter-Society Commission for Heart Disease Resources (*41*) also emphasized this point: "The overwhelming cause and effect relationship between smoking, bronchitis-emphysema and pulmonary heart disease is such that there is little doubt that a radical reduction or elimination of the cigarette habit would result in a greatly lowered incidence of the chronic respiratory diseases and cor pulmonale."

In recent studies, a decrease in the prevalence of respiratory symptoms among ex-cigarette smokers has been demonstrated (*10, 15, 75*). Higgins, et al. (*38*) interpreted data from 1957 and 1966 surveys of chronic respiratory disease in England as suggesting that the benefits of giving up smoking on respiratory symptoms are less in those who have smoked for many years than in those who have smoked for shorter periods.

Baker, et al. (*5*) undertook a therapeutic program for previously

unrecognized mild to moderate cases of COPD. One hundred thirty-four men were included in this study. Eighty-five percent of these men were cigarette smokers, 11 percent were ex-smokers, and 4 percent were nonsmokers. At the 6-month follow-up, 61 subjects were still in the treatment program. Patients were encouraged to stop smoking, and at the 6-month follow-up 34 percent of the cigarette smokers had stopped smoking, while 34 percent decreased their cigarette consumption by at least half. At the follow-up evaluation, approximately two-thirds of those who either gave up smoking or decreased their cigarette consumption showed improvement in symptoms. Thirty percent of those whose smoking habits did not change showed improvement in symptoms. No significant differences were found in the pulmonary function studies at the follow-up evaluation. Alteration of smoking habits was the single factor most closely related to symptomatic improvement.

Occupational Hazards

As observed by Bouhuys and Peters (*7*), the relative contributions of cigarette smoking and industrial exposure to the loss of lung function may at times be difficult to determine.

Recent studies in wool, textile, grain elevator, shipyard, pulp mill, steel, and underground mining industries have documented a higher prevalence of chronic bronchitis among cigarette smokers than nonsmokers (*9, 13, 19, 20, 39, 42, 47, 50*). Similar studies in steel, pulp mill, machine shop, and welding industries indicate a greater frequency of respiratory symptoms and/or diminished pulmonary function in smokers than in nonsmokers (*22, 23, 30, 39*).

Japanese investigators recently reported that former employees of a poison gas factory had a high prevalence of chronic bronchitis and expiratory slowing; a history of chronic bronchitis was obtained from 67 percent of smoking men and 47 percent of nonsmoking men who had manufactured mustard gas or lewisite (*54*).

In recent months several articles have been published on coal workers' pneumoconiosis. Because coal miners are not allowed to smoke at work, they must smoke their cigarettes during a shorter period of time than non-miners; nevertheless, the average coal miner smokes as many cigarettes a day as does the non-miner (*51*). Thus, his exposure tends to be more intense during the period in which he is smoking. Also, the documented hazard of chronic exposure to coal dust may be compounded by the deleterious effect of smoking on ciliary function.

Ashford, et al. (*4*) studied approximately 30,000 working coal miners in Great Britain. Their data suggest that smoking and pneumoconiosis act independently in the production of pulmonary symptoms.

A total of 801 working, anthracite coal miners from Pennsylvania were investigated by Tokuhata, et al. (*68*). Twenty-four percent of the smoking miners had pulmonary function impairment as compared with 11 percent of miners who did not smoke. Because the smokers developed their pulmonary function abnormalities after a much shorter underground work exposure, the authors suggested that smoking may significantly accelerate the development of pneumoconiosis among coal miners.

Rasmussen and Nelson (*61*) studied 368 soft-coal miners from the Southern Appalachian coal fields. All workers included in the study had been involved in the coal industry for at least five years. Miners with a smoking history of 30 pack-years or more showed a significant ($P < .01$) reduction of FEV_1 when compared to nonsmoking miners. Impairment of oxygen transfer was greater in both the 15 to 29.9 pack-year group and the 30 plus pack-year group than among the lifelong nonsmokers ($P < .01$).

One hundred sixty-two dyspneic soft-coal miners, who gave histories of lifelong abstinence from cigarette smoking, were examined by Rasmussen (*60*). Of these patients, 85.6 percent had some X-ray evidence of pneumoconiosis. The group as a whole was ". . . not representative of all coal miners, nor of all symptomatic coal miners." Even though 56 percent of these miners had "normal" ventilatory capacities, i.e., an FEV_1 which was 75 percent or greater of the predicted normal vital capacity, more than 90 percent had an alveolar-arterial oxygen gradient during exercise which exceeded 19.9 mmHg. In more than 95 percent of the "normal" group, this gradient was not associated with significant arterial oxygen desaturation during exercise. The loss of pulmonary function in the entire group of non-cigarette smokers was somewhat less than that found in a group of miners composed of cigarette smokers and nonsmokers; nonetheless, these findings demonstrate that, in the absence of cigarette smoking, coal dust exposure may be associated with abnormalities in oxygen transfer during exercise, despite the presence of a normal FEV_1.

An autopsy study of 144 Appalachian coal miners was carried out by Naeye, et al. (*53*). Several parameters of cardiac and pulmonary structure were examined with regard to the effect of smoking. The volume of pulmonary macules and nodules containing coal dust and the concentration of silica crystals and collagen in these macules and nodules were unrelated to smoking. Right ventricular hypertrophy, defined according to an index developed by Naeye, was present in all groups of miners but was more severe in the bituminous workers who smoked cigarettes. The emphysema index, which is a measurement of the percent of lung tissue comprised of abnormal air space, was determined only in bituminous coal miners. It was

significantly greater in cigarette smokers than in nonsmokers. Goblet cell hyperplasia, which appeared to be present in the entire group, was somewhat greater in the bituminous coal miners who smoked than in the nonsmokers, but the differences were not statistically significant.

Several investigators have concluded that cigarette smoking by itself is more important in the production of respiratory disease, other than pneumoconiosis, among coal miners than is exposure to coal dust (*24, 34, 58, 68*). Rasmussen questions this view (*60*). There is no consensus in recent publications on what role cigarette smoke may play in the development of coal workers' pneumoconiosis (*24, 51, 53, 58, 68*).

Weiss (*73*) examined 100 asbestos textile workers and found a greater prevalence of pulmonary fibrosis among cigarette smokers than nonsmokers. The prevalence increased with increasing amount and duration of cigarette smoking and with increasing duration of exposure to asbestos.

Genetic Factors

An infrequent genetic error, homozygous alpha$_1$-antitrypsin deficiency, has been commonly associated with the premature development of severe, panacinar emphysema. It is postulated that alpha$_1$-antitrypsin is essential to protect the lung against the destructive action of naturally occurring proteinases (*36*).

Related questions of current interest deal with the prevalence and significance of the heterozygous deficiency state (intermediate serum antitrypsin deficiency) and the interaction of smoking with the severe and intermediate deficiency states. Mittman, et al. (*49*) recently reviewed the limited data available on the smoking habits of patients with alpha$_1$-antitrypsin deficiency; the cigarette smoke exposure of patients with the intermediate deficiency appears to be greater than that of patients with the severe deficiency.

Cigarette smoking has been reported to be a possible precipitating factor in the development of COPD in the homozygous deficiency state (*40*). Some studies (*26, 44, 49, 67*) have demonstrated an association between the heterozygous deficiency state and the development of COPD, while other studies have not (*35,62*). Mittman, et al. (*49*) have suggested that the intermediate deficiency may predispose to lung disease by accentuating an individual's susceptibility to the harmful effects of external irritants. Whether or not cigarette smoking acts together with the homozygous or heterozygous deficiency states to increase the risk of developing either panacinar emphysema or the more common forms of COPD has not been adequately studied.

PATHOLOGICAL STUDIES

In previous investigations, a correlation has been found between cigarette smoking and the histologic changes characteristic of bronchitis and emphysema (*70*).

An autopsy study of 60 patients with COPD was performed by Cullen, et al. (*16*). Although they did not find a correlation between the smoking history, total emphysema score, type of emphysema, or bronchial histologic features, the authors noted that only three patients were non-cigarette smokers. These three patients were pipe or cigar smokers. Eight patients who had stopped smoking three years before death had the same bronchial histologic abnormalities as those who continued smoking until death. This suggests that the bronchial abnormalities had become irreversible at the time of smoking cessation.

Dunnill and Ryder (*21*) carried out a quantitative study of the relationship between chronic bronchitis, emphysema, and smoking. The lungs of 353 patients were examined at autopsy, and a smoking history was available in 179 cases. A small but significant ($P < .005$) difference was found between smokers and nonsmokers in the percentage volume of bronchial mucous glands. Emphysema, mainly the centrilobular type, was found significantly ($P < .001$) more frequently in men and women smokers than nonsmokers, and it occurred at a much younger age in the smokers.

EXPERIMENTAL STUDIES

HUMAN STUDIES

Anderson (*3*) observed in a few patients with and without COPD that cigarette smoking can produce V/Q (ventilation/perfusion) changes resulting in a significant average drop in PaO_2 (partial pressure of oxygen in arterial blood).

Clarke, et al. (*14*) studied the bronchoconstrictor effect of plain and filtered cigarettes in 16 men. Filtration of either the particulate or vapor phase of the smoke had a similar effect in reducing the bronchoconstrictor response to cigarette smoke inhalation.

Using a reference cigarette developed by the University of Kentucky, Diamond, et al. (*18*) measured pulmonary expiratory resistance immediately after smoking. Heavy smokers, whose control resistance values were significantly higher than those of moderate or nonsmokers, had a decrease in resistance, while nonsmokers had an increase. Although selected ventilatory function tests did not change significantly after smoking, the author noted that the methods used in this study are probably not sensitive enough to measure constriction in peripheral airways, where smoking is thought to exert an adverse effect.

Frasca, et al. (*32*) made electron microscopic observations in areas of fibrosis and emphysema of the lungs of dogs, which had been subjected to experimental cigarette smoking as reported by Hammond, et al. (*37*). Details of the smoking procedure were reviewed in the 1971 report, "The Health Consequences of Smoking" (*70*). The major findings in the study of Frasca, et al. were: a complete loss or marked reduction in the number of alveolar septal capillaries, a marked thickening of the alveolar septa due to increased amounts of collagen, thickening of the pleural stroma due to large amounts of collagen, and the presence of increased numbers of macrophages in both the pleura and parenchyma. Many of these macrophages were filled with pleomorphic cytoplasmic inclusions. Crystalline-like structures were found in membrane-bound inclusions and ferritin-like particles occurred both in large membrane-bound aggregates and lying free in the cytoplasm.

Flint, et al. (*29*) reported a significant increase in the number of polymorphonuclear leukocytes recoverable from the lungs of guinea pigs following exposure of these animals to cigarette smoke. Because no changes in serum alpha$_1$-antitrypsin levels were found in this setting, the authors hypothesized that an imbalance may occur between proteolytic enzymes released by polymorphonuclear leukocytes and the inhibitors of these enzymes.

The stress effects of forced mouth-breathing and inhalation of cigarette smoke on lung mitochondrial phosphorylation were studied in the guinea pig by Kyle and Riesen (*45*). Mouth-breathing alone was associated with impaired efficiency of phosphorylation at two mitochondrial loci, while mouth-breathing guinea pigs exposed to cigarette smoke lost efficiency at only one of these sites.

Aviado and coworkers have studied the effects of hormones on the pulmonary response to cigarette smoke inhalation and intravenous nicotine injection. Subcutaneous progesterone administration, prior to nicotine or smoke exposure, reduced the bronchoconstrictor response in rats (*64*). A similar experiment involving pretreatment of dogs with glucocorticoids resulted in variable bronchoconstrictor responses after exposure to cigarette smoke (*12*).

Nitrogen dioxide (NO_2), a gas found in cigarette smoke and some industrially polluted air, can destroy cellular membranes and subcellular structures (*25*). Continuous administration of low concentrations of NO_2 in rats has produced an emphysema-like disease (*66*). Falk has suggested that NO_2 may "... carry a major responsibility for the high incidence of emphysema in cigarette smokers" (*25*).

Stephens, et al. (*66*) examined ultrastructural changes in pulmonary connective tissue of rats exposed to 2 to 20 p.p.m. of NO_2 for

varying periods of time. In the absence of significant cell destruction, striking alterations in both collagen fibrils and basement membranes were found.

Overall Clearance

Pavia, et al. (*55, 56*) examined the effect of cigarette smoking on the mucociliary mechanism of the human lung. A temporary slowing of mucociliary clearance was found in a group of 22 elderly smokers (*56*). Eight of these subjects had mild restrictive impairment and two had airway obstruction. When percentage clearance by elderly cigarette smokers and nonsmokers was compared, significant differences were not demonstrable (*55*). In the latter study, patients with functional evidence of lung disease were not included.

Deposition and clearance of inhaled 2μ particles of iron oxide labeled with ^{198}Au were studied in 19 young, normal subjects by Lourenço, et al. (*46*). While tracheobronchial clearance began immediately after inhalation in nonsmokers, it was delayed for periods of 1 to 4 hours after inhalation in smokers.

Frances, et al. (*31*) studied the effect of cigarette smoke on particle transport on donkey nasociliary mucosa. This mucosa was found to be much more resistant to the effects of cigarette smoke than that in the donkey tracheobronchial tree. More recently, Albert, et al. (*2*) published a report that in one of three donkeys tolerance to cigarette smoke had developed in the tracheobronchial mucosa.

Weissbecker, et al. (*74*) examined *in vivo* mucus flow rates in cats exposed to cigarette smoke gas phase of varied composition. Several compounds, e.g., isoprene and nitrogen dioxide, when added in combination to the gas phase, were effective in reducing the mucus flow, compared to the effect of the gas phase alone. Other compounds, e.g., CO, diminished the mucostatic effect of the gas phase. Compounds producing mucostasis were ineffective when added to cigarette smoke. These experiments indicate that effects observed from pure compounds cannot be used to predict the effect of cigarette smoke on mucus transport.

Phagocytosis

The recent literature concerning the effect of tobacco smoke on macrophage function is reviewed in the chapter on allergy of this report.

Pratt, et al. (*59*) have extended their studies on the ultrastructure of human alveolar macrophages. Macrophages obtained from smokers tend to contain more heterogeneous inclusions than those from nonsmokers. Angular and needle-like structures were observed

only in the inclusions of smokers. The authors concluded that these structures "... may represent undigested smoke products...."

In an investigation of early emphysema found in patients who were autopsied, McLaughlin and Tueller (*48*) found brownish, pigmented alveolar macrophages in the intact parenchyma adjacent to areas of emphysema. Such macrophages were not found in normal lungs, but were found in sputum specimens of "... apparently healthy cigarette smokers." In heavy smokers many of the macrophages also contained iron particles.

THE SURFACTANT SYSTEM

Giammona, et al. (*33*) measured the surface tension of lung extracts and bronchial washings of dogs following exposure to cigarette smoke. Elevated minimal surface tension values were found in bronchial washings obtained from three dogs. The values remained elevated for 48 hours after the cigarette smoke exposure; the values obtained one week after the cigarette smoke exposure were normal. The surface tension measurements of lung extracts obtained from four autopsied dogs were normal.

OTHER RESPIRATORY DISORDERS

Finklea, et al. (*28*) studied acute, noninfluenzal respiratory disease in military cadets and found significantly higher incidence rates for acute upper and lower respiratory illness among cigarette smokers than nonsmokers. Intermediate rates were found for lighter cigarette smokers, cigar, pipe, and ex-smokers.

HIGHLIGHTS OF CURRENT BRONCHOPULMONARY INFORMATION

In addition to the comprehensive summary from the 1971 report, "The Health Consequences of Smoking" (*70*), cited earlier in this chapter, the following statements are made to emphasize the most recent developments in the field:

1. Recent epidemiological and clinical studies from several countries confirm that men and women cigarette smokers have an increased prevalence of respiratory symptoms and have diminished pulmonary function compared to nonsmokers.
2. Investigations of high school students have demonstrated that abnormal pulmonary function and pulmonary symptoms are more common in smokers than nonsmokers.

3. Recent occupational studies confirm that cigarette smoking is an important cause of COPD, acting both independently and in combination with occupational exposure.

4. Recent experimental studies confirm that cigarette smoking exerts an adverse effect on pulmonary clearance and macrophage function.

5. Pulmonary macrophages obtained from cigarette smokers exhibit characteristic morphologic differences when compared to those obtained from nonsmokers.

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