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# CHAPTER 2

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## Smoking and Chronic Bronchopulmonary Diseases (Non-Neoplastic)

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## INTRODUCTION

The primary purpose of the 1968 Supplemental Report is to review the pertinent literature that has become available subsequent to the 1967 report. Brief mention of the conclusions of the 1964 report and the highlights of the 1967 report is made to facilitate an understanding of the significance of the newer information. The current research findings should be considered in the perspective of the research evidence previously reported in the 1964 (59) and 1967 (57) reports.

### CONCLUSIONS OF THE 1964 REPORT (59)

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

2. A relationship exists between pulmonary emphysema and cigarette smoking but 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 nonsmokers.

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

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.

### HIGHLIGHTS OF THE 1967 REPORT (57)

1. New data confirm and to some extent strengthen the conclusions of the Surgeon General's 1964 Report.

2. Cigarette smoking is the most important of the causes of chronic non-neoplastic bronchopulmonary diseases in the United States. It greatly increases the risk of dying not only from both chronic bronchitis but also from pulmonary emphysema.

3. Cessation of smoking is followed by a reduction in mortality from chronic bronchopulmonary disease relative to the mortality of those who continue to smoke.

4. Even relatively young cigarette smokers frequently have demonstrable respiratory symptoms and reduction in ventilatory function.

### GENERAL BRONCHOPULMONARY DISEASE MORTALITY AND MORBIDITY

The 1967 report (57) pointed out the alarming rate of increase in emphysema and/or chronic bronchitis mortality (table 1). There were 25,416 deaths from emphysema and/or chronic bronchitis in 1966 which represent a 25 percent increase over 1964. The increasing death rates for chronic bronchitis and emphysema since 1950 are shown in figure 1. Death rates for these diseases are increasing more rapidly than are the death rates for lung cancer as illustrated in figure 2.

Last year, payments made by the Social Security Administration to men and women totally disabled because of emphysema amounted to about 90 million dollars; this was 7 percent of all disability payments, making chronic lung disease second only to heart disease in this regard.

TABLE 1.—*Mortality from emphysema and/or chronic bronchitis: United States, each year 1950-1964*

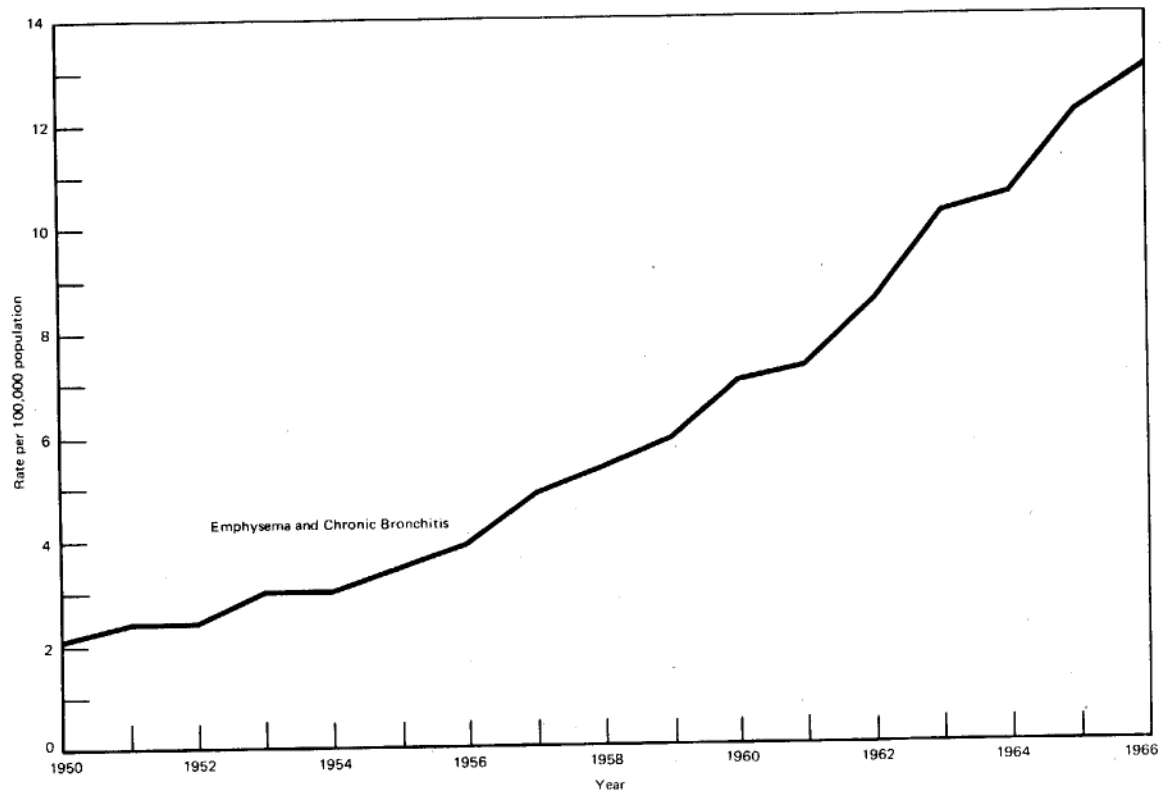
[ISC codes 501, 502, 527.1]

Year	Number of deaths	Year	Number of deaths	Year	Number of deaths
1950	3, 157	1955	5, 616	1960	12, 426
1951	3, 660	1956	6, 535	1961	13, 302
1952	3, 846	1957	8, 136	1962	15, 915
1953	4, 657	1958	9, 328	1963	19, 443
1954	4, 877	1959	10, 433	1964	20, 208

SOURCE: Vital Statistics of the United States, 1950-1964 (58).

### POPULATION STUDIES

Several papers published in the past year reported the results of surveys of pulmonary function and respiratory symptoms in different populations. All of those which were reviewed and which included a comparison of findings between smokers and nonsmokers reported similar observations. In all instances, smokers had respiratory symptoms such as cough, phlegm production, and dyspnea more often than nonsmokers or ex-smokers of the same age and sex. In surveys which included pulmonary function tests, it was found that smokers did not perform as well as nonsmokers or ex-smokers. Substantially, these observations confirm those of earlier years without indicating new associations.



**FIGURE 1—Death rates for emphysema and chronic bronchitis. United States, 1950–1966 (Arithmetic scale).**  
**SOURCE: National Center for Chronic Disease Control.**

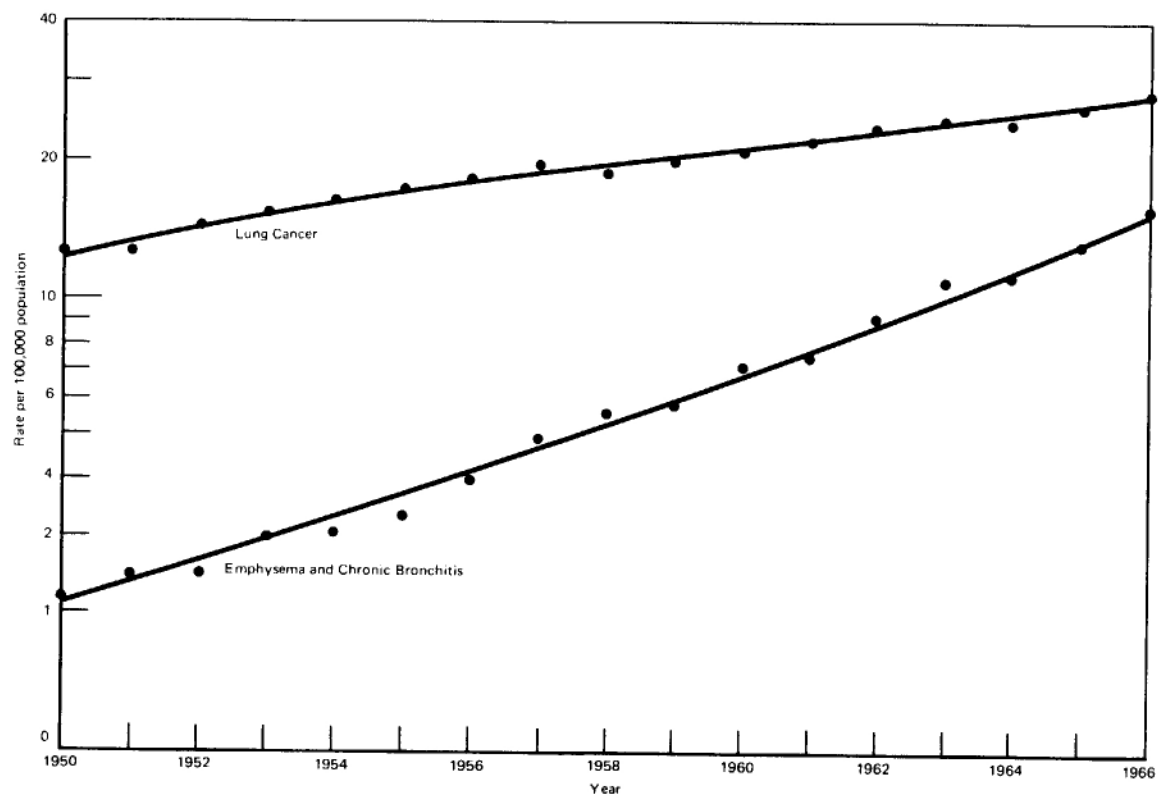


FIGURE 2—Death rates for emphysema and chronic bronchitis and for lung cancer : United States, 1950–1966 (Logarithmic scale).  
SOURCE: National Center for Chronic Disease Control.



A few specific surveys might be mentioned. Huhti (27) surveyed 1,028 men and women in a village in Finland. None of the women smoked. In men the one-second forced expiratory volume ( $FEV_{1.0}$ ) and the peak expiratory flow (PEF) were significantly lower among those men who smoked 15 or more cigarettes a day than those who smoked less or not at all. No difference in forced vital capacity (FVC) was observed.

Edelman, et al. (14) studied 410 men and found lower values of  $FEV_{1.0}$ , FVC, and maximal voluntary ventilations among current smokers than among nonsmokers. They also reported an inverse relationship between the number of cigarettes smoked and pulmonary function.

Stanek, et al. (54) noted a definite association between chronic cough and phlegm production (chronic bronchitis) and cigarette smoking among a random sample of 443 men surveyed in Prague. Freour, et al. (21) in Bordeaux also reported a much greater frequency of symptoms of chronic bronchitis among smokers than nonsmokers in a preliminary report based on 1,055 examinations.

Higgins and his associates (25) reported observations from a nine year followup study of men in an industrial town in England. Among the 385 men who were age 55-64 at the start of the study, mortality during the nine years was twice as high for smokers as nonsmokers. Ex-smokers had the same mortality experience as nonsmokers. Among the survivors of all ages who were tested initially and nine years later, the average decline in lung function as measured by the  $FEV_{.75}$  was smallest in nonsmokers, slightly greater in ex-smokers, and greatest in smokers. The findings suggested that smoking was a more important factor than occupation in respiratory disability.

Industrial air pollution studies have been performed by Lowe (32) using a population of steelworkers at Ebbw Vale and Port Talbot, with smoking and chronic bronchitis data presented in a subsequent publication (31). It was noted that for each age group, chronic bronchitis was about three times more prevalent among men who smoked 25 or more cigarettes per day, than among those who had never smoked. Cigarette smokers appear to be more adversely affected by pulmonary exposure to dusts at work than the nonsmokers. The authors pointed out that studies to evaluate the interaction between smoking and industrial air pollution require occupational subgroups large enough to permit standardization for both age and smoking habits. In this way, the interaction between smoking and other air pollutants can be analyzed more definitively.

Most surveys have been of adults, but Holland, et al. (26) reported the findings of an investigation of smoking and respiratory symptoms among more than 10,000 school children, age eleven or more, in England. The survey was conducted in 1965 and repeated in 1966. Ciga-

rette smokers (at least one cigarette per week) more frequently reported symptoms of cough and phlegm production than nonsmokers and the prevalence of symptoms increased with increases in the amount smoked. Children who smoked one year but did not smoke in the subsequent year had a lower frequency of symptoms in the second year.

#### RELATIONSHIPS TO PULMONARY INFECTION

The relationship between smoking and pulmonary infection is unclear. It is evident that cigarette smoking is a major cause of chronic bronchitis. Much of the symptomatology of chronic bronchitis of smokers, particularly cigarette smokers, results from the harmful effects of inhaled tobacco smoke on the bronchial ciliary apparatus and the mucous glands. These effects tend to impair mucous removal from the bronchial and bronchiolar airways and possibly may, in turn, increase susceptibility to pulmonary infections.

In a study of 191 boys, age 14 to 19, in a preparatory school, the incidence of all respiratory illness over a one-year period was positively correlated with smoking habits within each age group. "Severe" (purulent sputum) lower respiratory tract illnesses were nine times more frequent in regular smokers than nonsmokers (age-adjusted) (24).

A study in Cairo of the relation between smoking and infection and appearance of mucous gland hypertrophy in the main bronchi was reported by Megahed and his colleagues (34). They studied 50 men with chronic bronchitis and found substantially more mucous gland hypertrophy among the 43 smokers than the 7 nonsmokers. This hypertrophy seemed unrelated to the presence of potential pathogenic organisms isolated from a single bronchial lavage, although the authors believed that infection might have an initiating or potentiating effect.

Fletcher (17) studied the relationship between frequency of respiratory illness as measured by sputum purulence and histories of "chest illnesses" and "chest colds" and the rate of decline of FEV in slightly more than 900 men who were followed at least four years. He concludes that illnesses and sputum purulence have no significant effect on FEV regression. (This study will be discussed again later in this chapter).

It appears that, in patients with chronic obstructive bronchopulmonary disease caused by cigarette smoking or other pulmonary irritants, superimposed infections may cause exacerbations of the chronic disease process. There is no substantial evidence that infections per se cause much of the chronic obstructive bronchopulmonary disease seen in cigarette smokers.

Wynder (62) reported that the hyperplastic and metaplastic effects of Swine influenza virus could not be enhanced by subsequent exposure

of mice to cigarette smoke. Previous literature indicates that the sequence of events may be of some importance, since there have been reports that cigarette smoke increases the bronchial epithelial reaction to influenza virus. Spurgash (53) reported that pre-exposure to cigarette smoke did not have any significant effect on resistance of mice to subsequent influenza virus infection inoculated by aerosol inhalation. But, the subsequent exposure of pre-infected mice to cigarette smoke resulted in significantly higher mortality rates, thus suggesting that cigarette smoke can aggravate an existing respiratory viral infection. However, smoke-exposed mice subsequently challenged with certain bacteria, *Klebsiella pneumoniae* or *Diplococcus pneumoniae*, also exhibited a decreased resistance to respiratory infection as shown by a decreased survival time and a higher mortality (53).

The tobacco plant can be diseased by a variety of fungi (33). Of these the *Alternaria* species and *Aspergillus niger* were recently shown to increase the toxicity of cigarette smoke (20). Mice exposed to smoke from hay previously inoculated with *Alternaria* or *Aspergillus niger*, showed progressive pulmonary congestion, edema and tissue destruction confirmed by autopsy. Those mice in a hay-smoke control group were normal clinically and showed only chronic pulmonary inflammation on autopsy.

## SMOKING AND BRONCHOPULMONARY PHYSIOLOGY

### ANIMAL AND EXPERIMENTAL STUDIES

The ciliotoxic effects of cigarette smoke were presented in the 1964 (59) and 1967 Reports (57). Discussants in a recent symposium (29), pointed out that both volatile and particulate components of cigarette smoke can adversely affect ciliary activity. In short-term *in vivo* experiments, Dalhamn (11) showed that the ciliostatic effect of cigarette smoke was directly related to the "tar" content if the gas phase was held constant.

Rylander (44) reported that in guinea pigs exposed to cigarette smoke, the reduction of killed, radioactive bacteria was lower than in controls, presumably due to a decrease in mucus flow. There was no significant difference in reduction of viable bacteria.

A study by Dalhamn, et al. (10) suggests that lack of oxygen in the external environmental *in vitro* can reduce ciliary activity. The main problem in the evaluation of studies related to ciliary activity is to determine to what extent the *in vitro* studies can relate to the *in vivo* studies in animals and in man. For instance, the ciliotoxic effects of hydrogen cyanide in cigarette smoke were dose-related in experiments on clam gills *in vitro*, but the same results could not be reproduced with *in vivo* experiments in cats (12). Volatile (gas phase) components have been shown to be retained to a large extent by wet surfaces (28),

which raises the question of how much of the volatile ciliotoxic agents in cigarette smoke entering the moist oral cavity actually enter the lower respiratory tract.

Davis, et al. (13) in experiments with respiratory irritants including cigarette smoke in guinea pigs, have implicated the nasopharynx and larynx as sources of receptor stimulation leading to increased upper airway resistance, and decreases in respiration rate and minute volume. These effects were not present when a tracheostomy was performed to bypass the smoke directly into the trachea. However, Guillermin (23) noted increased airway resistance and decreased compliance in the tracheotomized and spinal guinea pig after smoke inhalation.

Aviado and his co-workers (2, 3, 4, 19, 38, 45, 46, 47, 48) have continued their studies on bronchoconstriction and bronchodilation in animals and recently have further investigated the role of histamine in a study of inhibitors for histamine decarboxylase in rabbits, dogs, and cats (39). These species have variations in response to cigarette smoking as previously noted. Cats have a uniphasic bronchoconstrictor response to inhaled cigarette smoke (somewhat like man's) and dogs have a biphasic response. Rabbits were observed to behave differently than cats or dogs. Histamine has been implicated as mediating part of the bronchoconstrictive effect of cigarette smoke. The rabbit does not respond to histamine by bronchoconstriction. This study (39) suggests that the rabbit lacks a histamine sensitive system in the airways, in contrast to cats and dogs. Alpha-hydrazino histidine, which inhibits the enzyme histamine decarboxylase, was demonstrated to prevent much of the bronchoconstrictive effect in cats and dogs. By analogy, this suggests the possibility that histamine may mediate some of the bronchoconstrictive response to inhaled tobacco smoke noted in humans. Pretreatment with atropine has been shown to block the bronchoconstriction caused by cigarette smoke (36) and by histamine inhalation in humans (7, 8, 52).

There is experimental evidence (48) in dogs, that the pulmonary exposure to inhaled cigarette smoke or injected nicotine can result in pulmonary vasoconstriction, causing increased pulmonary arterial pressure. This effect is thought to be due to histamine release from lung tissue (48). Autopsy studies in humans, by Auerbach (1), showed considerably greater fibrous thickening of the arterioles and small arteries in smokers, occurring not only in the lungs, but other organs as well. The degree of fibrous thickening increased with age and the amount of cigarette smoking.

Participants in a recent international symposium on the mechanism of elimination of deposited particles from the lungs (15), discussed the relationships among alveolar surfactant, alveolar macrophages, the alveolar transport mechanisms, and the mucociliary apparatus; which may also relate to the pathoetiology of pulmonary emphysema.

Giammona (22) reports that cigarette smoke consistently lowers the maximal surface tension without altering the minimal surface tension of lung extracts after *in vitro* exposure to cigarette smoke. *In vivo* changes were noted in guinea pigs, but not in dogs or cats, which he thought may have been due to insufficient exposure. Additional information concerning surfactant has been discussed by Sekulic, et al. (49, 50). Yeager, et al, (63) have reported that cigarette smoke has a depressant effect on protein synthesis of human alveolar cells *in vitro*.

#### STUDIES IN HUMANS

Fletcher (17) in the study mentioned earlier in this chapter, correlated the rate of decline of FEV in over 900 men followed for at least four years, with respect to starting FEV, cigarette smoking, sputum purulence, and histories of respiratory infections. He tested FEV's in response to the acute effect of smoking cigarettes, and found that the mean regression of FEV in those subjects who had a higher prevalence of cough and sputum was not significantly different from those with a lower prevalence. The men with higher initial standardized levels of FEV had less steep regressions than those with lower levels. Cigarette smoking had a significant effect on decline of FEV. Sputum eosinophilia was also related but apparently to a lesser degree, and Fletcher stated that there was no confirmation of the possible role of tobacco allergy in chronic obstructive bronchitis. With regard to the decline in FEV, more information on controls and on the quantity of cigarettes usually smoked would be helpful. While contributing important information, this study does not fully describe the progression of declining FEV in cigarette smokers in relation to the quantity that they smoked before and over the time-period studied. In a detailed study of 58 bronchitics (50 of whom had positive smoking histories) Simonsson (51) found a positive correlation between the degree of obstructive status and the reactivity to exposure to nebulized acetylcholine; and noted that a larger decrease in airflow seems to occur in previously obstructed airways than in normal ones.

Peterson (42) studies pulmonary function in a group of 12 individuals who had stopped cigarette smoking for 18 months, and compared their pulmonary function test before and after cessation. These individuals showed significant improvements in their pulmonary functions as measured by timed vital capacity and expiratory flow rates. Ex-smokers reported a decrease in cough and breathlessness after cessation of smoking. (This study confirms the findings of Krumholz reported in the 1967 report). The mean FEV of Peterson's ex-smokers was markedly greater than that observed in another group of individuals who had continued to smoke cigarettes during the same 18 month period, measured at the same time intervals.

Wilhelmsen (60) found in a small study of 16 persons who had smoked over 10 cigarettes a day for a mean of 25 years that cessation of cigarette smoking for an average of 40 days was accompanied by a marked decrease of sputum production, coughing and wheezing, and a significant increase in FEV<sub>1</sub>.

Bates (5,6) has reviewed the reliability and constancy of pulmonary function tests. He notes the importance of making pathological diagnoses with lungs inflated at autopsy. Morphologic considerations of emphysema are correlated with functional abnormalities and current biochemical research. He discusses derangement of pulmonary ventilation-perfusion distribution in relation to bronchial and/or alveolar damage from cigarette smoking with consequent stresses on right ventricular function. He emphasizes the fact that obstructive bronchitis appears to lead more frequently to right heart failure than does "pure" emphysema.

Although instances of "pure" emphysema or "pure" bronchitis exist, most patients with respiratory obstruction appear to have both emphysema and bronchitis. Bates suggests the theory that one of cigarette smoking's harmful effects may be destruction of bronchiolar structure. This could lead to disturbed ventilation-perfusion (V/Q) relationships. As enough lung tissue breaks down, causing centrilobular emphysema, there is impairment of gas equilibration within the centrilobular spaces. Increasing derangement of the V/Q distribution in turn can lead to hypercapnia and hypoxemia. Clinically, what may seem to be respiratory decompensation, may actually be incipient cardiopulmonary decompensation due to the deranged V/Q and gas imbalance resulting from the obstructive bronchiolitis.

Postural hypoxemia has also been noted (55) in young asymptomatic cigarette smokers with no evidence of chronic lung disease when in the supine position as compared with nonsmoking controls.

#### THEORIES INTERRELATING CIGARETTE SMOKING AND CHRONIC OBSTRUCTIVE BRONCHOPULMONARY DISEASE WITH PULMONARY HYPERTENSION AND COR PULMONALE

Hypercapnia and hypoxemia are capable of causing pulmonary vasoconstriction with a resultant increase in pulmonary arterial pressure and right ventricular work. Stuart-Harris, in a review article (56), relates these phenomena to the clinical picture of pulmonary hypertension and right heart failure seen in patients with pulmonary insufficiency caused by chronic obstructive bronchitis. Since the pathologic changes in the small pulmonary vessels are not usually as severe as those found in congenital heart disease, it is believed that the pulmonary hypertension seen in chronic obstructive lung disease is of the vasoconstrictive type. Although most patients with severe chronic

bronchitis have some emphysema, it is the airway obstruction of chronic bronchitis which may relate most strongly to the development of cor pulmonale. It is now apparent that cor pulmonale can be a sequel to severe obstructive bronchitis without emphysematous changes (9, 17, 35, 37). Studies (16, 18, 43) indicate that patients with hypercapnia and hypoxemia due to abnormal pulmonary ventilation-perfusion relationships are likely to develop cardiac complications. As indicated in the preceding section of this report, recent studies (40, 41, 43) have demonstrated the presence of ventilation-perfusion imbalances in patients with chronic bronchitis—the extent of imbalances being related to the severity of bronchitic process. Penman, et al. (41) determined the gas tensions in expired air and arterial blood and used them to calculate the alveolar dead space and alveolar blood shunt, permitting estimation of three theoretical “compartments” of the lung: (1) Ventilated but unperfused (alveolar dead space) “compartment,” (2) unventilated perfused (alveolar blood shunt) “compartment” and (3) “normal” ventilated perfused “compartment.” Chronic bronchitis were found to have abnormalities of ventilation and perfusion with a marked reduction in the “normal” “compartment.” In patients with decompensated cor pulmonale, further studies of the correlations between cardiac output, arterial oxygen tension, and arterial carbon dioxide tension with the above “compartments” lead Penman, et al. (41) to believe that in cases of decompensated cor pulmonale a considerable fraction of the cardiac output is shunted without exposure to aerated alveoli.

It was further hypothesized that this increased shunting of blood through non-aerated regions of lung would result in increasing hypoxemia and hypercapnia with consequent further constriction of the pulmonary vasculature and further encroachment of the alveolar dead space upon the normally ventilated and perfused lung. Williams, et al. (61) in determining the acute effects of cigarette smoking, found an increase in the “alveolar dead space” in 11 patients with obstructive airway disease. They postulate this to be due to “the effect of nicotine on the vasculature of the lung in this group of patients.”

Since pulmonary vasoconstriction will also increase the pulmonary arterial pressure and right ventricular work, it may also lead to right ventricular failure and the classic picture of cor pulmonale. The beneficial effects of correcting (to the extent that this is possible) the ventilatory problems in these patients is well known, and it is thought that the basis of the improvement is the correction of the hypoxemia and hypercapnia which allows a reversal of the pulmonary vasoconstriction, thereby permitting better perfusion of underperfused areas and also decreasing the workload of the right ventricle. Stuart-Harris also pointed out that the relief of myocardial anoxia with appropriate therapy may help the right ventricle recompensate.