Evidence that this mechanism may occur in humans is provided by the findings of Parving (*50*) who showed an increased transcapillary escape rate for ^{131}I-labeled albumin in humans exposed to .43 percent CO (COHb 20 percent) for 3 to 5 hours, but not in those made hypoxic to an altitude of 4300 meters (hemoglobin 75 percent saturated).

By exposing rabbits to different concentrations of carbon monoxide (50, 100, and 180 ppm) for varying periods (.5, 2, 4, 8, 24, and 48 hours), Thomsen and Kjeldsen (*59*) were able to show a threshold of 100 ppm of CO for myocardial damage. The demonstration of damage at this level of CO (COHb 8-10 percent) is possibly explained by the ratio of carboxymyoglobin to carboxyhemoglobin which is about 3 to 1 in myocardium at ambient Po_2. Thus, a COHb level of 10 percent would be accompanied by a carboxymyoglobin level of 30 percent in heart muscle. This ratio is even greater under hypoxic conditions with a ratio of 6 to 1 when the arterial Po_2 is below 40 mm Hg (*15*).

Nicotine

In a study of the effects of smoking cigarettes with low and high nicotine content, Hill and Wynder (*30*) noted increasing serum epinephrine levels with increasing nicotine content of the smoke, but serum norepinephrine levels were unchanged. However, increasing serum epinephrine levels with increasing number of low nicotine content cigarettes smoked were also noted.

Acrolein

Egle and Hudgins (*21*) did inhalation studies with acrolein on rats. Inhalation of this aldehyde at concentrations below those encountered in cigarette smoke resulted in a significant increase in blood pressure and heart rate in rats.

CEREBROVASCULAR DISEASE

There has been conflicting evidence on whether there is an increased risk of cerebrovascular disease due to smoking (*61, 62, 63, 64, 65, 66, 67, 68*). A prospective study by Paffenbarger, et al. (*48*) of 3,991 longshoremen followed for 18 years showed no correlation between fatal strokes and smoking. However, both the Dorn study of

U.S. veterans (*33*) and Hammond's study of one million men and women (*25*) showed a small but significant increase in the death rates from cerebrovascular disease among cigarette smokers. The Framingham 18-year followup of men ages 45 to 54 (*42*) and Paffenbarger's study of men who entered Harvard between 1916 and 1940 (*49*) also showed an excess risk of cerebrovascular disease associated with cigarette smoking.

Two recent studies provided more data on this topic. Ostfeld, et al. (*46, 47*), in a study of 2,748 people ages 65-74 receiving old age assistance in Cook County, Illinois, were unable to find any relation between cigarette smoking habits at the start of the study and incidence of new strokes or prevalence of transient ischemic attacks. Nomura, et al. (*44*), in a study of the population of Washington County, Maryland, ages 25 and older, were unable to find any relation between cigarette smoking and either mortality or morbidity from stroke. Nomura noted that "in atherosclerotic strokes the Framingham study and Paffenbarger's investigation of former college students included a great percentage of stroke cases under the age of 55. Because these two studies found an association between cigarette smoking and atherosclerotic strokes and the present study did not, it may be that the association is age-dependent."

Hammond (*25*) provides some data which may clarify this relationship. Analysis of his data shows that the difference between cerebrovascular death rates in cigarette smokers and nonsmokers increases as persons get older except in males ages 75-84 (Table 7), indicating that the excess death rates associated with cigarette smoking increase with advancing age. The ratio of the death rates for smokers and nonsmokers (mortality ratio), however, decreases with age, reflecting the fact that cerebrovascular disease death rates attributable to other causes increase with age more rapidly than death rates attributable to smoking. Cigarette smoking may well be a risk factor for stroke at all ages, but other causes of strokes become proportionally so important in older age groups that in studies not based on very large populations the risk due to cigarette smoking is masked by the large total number of strokes due to other causes.

TABLE 7. – *Age-standardized deaths rates and mortality ratios for cerebral vascular lesions for men and women by type of smoking (lifetime history) and age at start of study*

Type of Smoking	Age Groups			
	45–54	55–64	65–74	75–84
	CVL Death Rates per 100,000 Person-Years			
Men				
Never smoked regularly	28	92	349	1,358
Pipe, cigar	25	100	369	1,371
Cigarette and other	28	129	361	990
Cigarette only	42	130	477	1,168
Total	35	116	391	1,272
Women				
Never smoked regularly	18	57	228	1,082
Cigarette	38	88	315	1,277
Total	25	64	238	1,091
	CVL Mortality Ratios			
Men				
Never smoked regularly	1.00	1.00	1.00	1.00
Pipe, cigar	0.89	1.09	1.06	1.01
Cigarette and other	1.00	1.40	1.03	0.73
Cigarette only	1.50	1.41	1.37	0.86
Women				
Never smoked regularly	1.00	1.00	1.00	1.00
Cigarette	2.11	1.54	1.38	1.18

NOTE. – CVL = Cerebral vascular lesions.

EFFECTS OF SMOKING ON THE COAGULATION SYSTEM

Several studies have contributed to an understanding of the role of smoking in thrombogenesis. Levine (*41*), in a controlled double blind study, showed that smoking a single cigarette increased the platelet's response to a standard aggregating stimulus (ADP). This phenomenon did not occur when lettuce leaf cigarettes were smoked and was independent of a rise in free fatty acids in the plasma. The author postulates that this may be due to increasing epinephrine levels.

These data may have relevance for two other studies. In the clinical trial of the possible prevention of heart attack by hyperlipidemic drugs in Newcastle, England, (*19*) it was found that cigarette smokers were at increased risk of sudden death. This increased risk was not present in smokers treated with clofibrate. However, the researchers were unable to relate this reduction in risk to any effect of clofibrate on serum lipids. Recently Carvalho, et al. (*14*) evaluated 29 patients with familial hyperbetalipoproteinemia and noted that their platelets had an increased sensitivity to aggregating stimuli (ADP). Treatment with clofibrate returned the ADP sensitivity to normal without significantly altering serum lipids. This demonstrated effect of clofibrate may provide some insight into the Newcastle study. The reduction in the excess risk of sudden death could be due to a clofibrate induced reversal of increased sensitivity to aggregating stimuli produced by smoking.

SUMMARY OF RECENT CARDIOVASCULAR FINDINGS

1. Data from one recent incidence study suggest that cigarette smokers are more likely to develop hypertension than are nonsmokers. There is some evidence that suggests that stopping smoking may be accompanied by a rise in blood pressure.

2. Cigarette smoking has been shown to be the major source of elevated carboxyhemoglobin levels, with occupational exposure and air pollution being far less important in most circumstances. Carboxyhemoglobin levels in cigarette smokers are two to three times the levels in nonsmokers and increase with the amounts smoked.

3. Elevated carboxyhemoglobin levels have been shown to decrease maximal oxygen uptake in healthy people as well as to decrease the exercise tolerance of persons with angina pectoris and intermittent claudication. The carboxyhemoglobin levels at which these effects take place are well within the range produced by cigarette smoking.

4. Carbon monoxide at levels of exposure commonly reached by cigarette smokers has been shown to decrease cardiac contractility in persons with coronary heart disease.

5. Carbon monoxide has been shown to produce changes like those of early atherosclerosis in the aortas of rabbits.

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Chapter 3

Chronic Obstructive Bronchopulmonary Disease

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Contents

FIGURES

LIST OF TABLES

(A indicates tables located in appendix at end of chapter)

LIST OF TABLES (Continued)

(A indicates tables located in appendix at end of chapter)

INTRODUCTION

Chronic obstructive bronchopulmonary disease (COPD) is characterized by chronic obstruction to airflow within the lungs. The term COPD refers to three common respiratory ailments; namely, *chronic bronchitis, pulmonary emphysema, and reversible obstructive* lung disease (bronchial asthma).*

Chronic bronchitis has been defined as the chronic or recurrent excessive mucus secretion of the bronchial tree. It is characterized by cough with the production of sputum on most days for at least three months in the year during at least two consecutive years (217).

Pulmonary emphysema is that anatomically defined condition of the lung characterized by an abnormal, permanent increase in the size of the distal air spaces (beyond the terminal bronchiole) accompanied by destructive changes (*217*).

Patients can suffer from both of these conditions simultaneously. The symptoms as well as the abnormalities in pulmonary function observed in the presence of the two ailments may be quite similar. Patients with chronic bronchitis suffer from productive cough with or without dyspnea (breathlessness both at rest or on exertion) while pulmonary emphysema is characterized mainly by dyspnea. COPD comprises a spectrum of clinical manifestations; thus, it is frequently difficult to determine whether a particular patient is suffering from one of the two specified diseases alone or which one predominates when both are thought to be present.

COPD is responsible for significant mortality in the United States. In 1967, a total of 21,507 men and 3,885 women were recorded as dying from chronic bronchitis and emphysema (*221*). This figure does not include a sizable number of individuals for whom COPD was a contributory cause of death.

During the past two decades, a major increase has taken place in the mortality from COPD in the United States. In 1949, the death rate from COPD was 2.1 per 100,000 resident population, while in 1960 it was 6.0 (*222*), and in 1967, 12.9 (*221*). Although

* Because mortality from bronchial asthma does not appear to be related to cigarette smoking, the term COPD will be used henceforth to refer only to chronic bronchitis and pulmonary emphysema. Exacerbation of pre-existing bronchial asthma has been observed among cigarette smokers. Further elaboration of this question may be found in a previous Public Health Service Review (*223*).

much of this rise is probably due to changes in certification and recording methods as well as to an increased interest on the part of the medical community, an appreciable proportion is also generally accepted as reflecting a real increase in disease. Similar increases over the past 20 to 30 years have also been observed in Canada (*7*) and in Israel (*54*). The lack of a similar increase in Great Britain, a country with an extremely high rate of COPD, may be the result of a number of factors including improved therapy and decreased air pollution. Moreover, it is also likely that the diagnosis of COPD has been made more commonly and accurately in Great Britain for a longer time than in the United States, or elsewhere. Furthermore, the British definitions of bronchitis and emphysema have differed in the past from those used in the United States.

The mortality from and prevalence of COPD is probably underestimated. In a study of death certificates, Moriyama, et al. (*170*) reported that COPD is often omitted as a contributing cause of death. In a study of more than 350 autopsies, Mitchell, et al. (*169*) noted that the disease often goes unreported and that emphysema was occasionally found unassociated with severe clinical airway obstruction. Hepper, et al. (*110*) observed that ventilatory test results were abnormal in 10 percent of 714 patients in whom no symptoms, signs, or past history of pulmonary disease were noted. They concluded that severe degrees of ventilatory impairment may be undetected by history and physical examination alone. Boushy, et al. (*40*) evaluated clinical symptoms, physiologic measurements of airway obstruction, and morphologic bronchial and parenchymal changes in 90 males with bronchogenic carcinoma. The authors found that when either clinical, physiologic, or pathologic evidence of COPD was used alone, one-third to one-fourth of the patients were considered normal, but when all three criteria were used together, only one patient was free of COPD. The importance of COPD as a contributing cause of mortality is now beginning to be more fully recognized.

Clinicians have long observed that the majority of their patients suffering from COPD were cigarette smokers (*1, 150*). Epidemiological studies have validated this impression by indicating that cigarette smokers are at a much greater risk of developing or dying from this disease and that the risk increases with increased dosage of cigarette smoke, reaching in the smoker of two packs or more a day a level as high as 18 times that of the nonsmokers (*132*). The salutary effect of giving up smoking has also been borne out by clinical observation and epidemiological studies.

In a number of studies, smokers were found to suffer more frequently than nonsmokers from pulmonary symptoms including

cough, cough with production of phlegm, and dyspnea. By a variety of pulmonary function tests, smokers were shown to have diminished function as compared to nonsmokers and also to have a steeper slope of the expected decline of function with age. Tests of ventilation/perfusion relationships in the lung have revealed abnormal function in smokers. Autopsy studies have indicated that smokers dying of causes other than COPD have significantly more changes characteristic of emphysema than nonsmokers.

Several recent studies have validated the clinical impression that among patients who undergo surgery, cigarette smokers run a greater risk of developing complications in the post-operative period than nonsmokers.

Abundant experimental evidence of the role of smoking in bronchopulmonary disease has been obtained from experiments employing animals and tissue and cell cultures. Recent work has demonstrated, in dogs trained to inhale cigarette smoke through a tracheostoma, that emphysema, pulmonary fibrosis, and other pathologic changes in the pulmonary parenchyma and bronchi develop and that these changes are proportional to the total dosage of cigarette smoke inhaled. *In vivo* and *in vitro* studies have shown that whole cigarette smoke, or certain fractions thereof, inhibit ciliary activity of the bronchial epithelium, adversely affect the mucous sheath, and inhibit the phagocytic activity of the pulmonary alveolar macrophage. These abnormalities lead to retarded clearance of inhaled foreign matter including infectious agents from the lungs, thus predisposing the individual to respiratory infections. Evidence also exists that pulmonary surfactant may be adversely affected by cigarette smoke.

The convergence of these lines of evidence, which will be described in more detail in the body of this chapter, leads to the judgment that cigarette smoking is the most important cause of COPD in man.

EPIDEMIOLOGICAL STUDIES

COPD Mortality

Numerous epidemiological studies, based on a variety of populations and carried on in a number of countries, have investigated the association between cigarette smoking and COPD. They have shown a greatly increased mortality and morbidity from COPD among smokers as compared to nonsmokers. Results from the major prospective studies relating smoking and COPD mortality are presented in table 1. The majority of the studies separate

TABLE 1.—*Chronic obstructive bronchopulmonary disease mortality ratios*
(Actual number of deaths shown in parentheses)[1]
SM = Smokers. NS = Nonsmokers

PROSPECTIVE STUDIES								
Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths	Cigarettes/day pipes, cigars	Chronic bronchitis	Emphysema	Other
Hammond and Horn, 1958, U.S.A. (*105*).	187,783 white males in 9 states 50-69 years of age.	Questionnaire and follow-up of death certificate.	3½	338 SM .....308 NS 30	*Cigarettes* NS .....1.00 (30) <10 .....1.67 (10) 10-20 .....3.00 (57) >20 .....3.64 (40) All .....2.85 (231) *Pipes* NS .....1.00 (30) SM .....1.77 (23) *Cigars* NS .....1.00 (30) SM 1.29 (18)			
Doll and Hill 1964 Great Britain (*70*).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	292 *Chronic bronchitis* 111 *Other* 181		*Cigarettes* NS .....1.00 1-14 .....6.80 15-24 ...12.80 >25 .....21.20 All .....11.60 *Pipes and Cigars* SM 3.00		Cigarettes NS .....1.00 1-14 ....0.65 15-24 ..1.08 >25 ....0.63 All .....0.81 *Pipes and Cigars* SM 0.78

TABLE 1.—*Chronic obstructive bronchopulmonary disease mortality ratios (cont.)*

(Actual number of deaths shown in parentheses)[1]

SM = Smokers. NS = Nonsmokers

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths	Cigarettes/day pipes, cigars	Chronic bronchitis	Emphysema	Other
				PROSPECTIVE STUDIES				
Best, 1966, Canada (*90*).	Approximately 78,000 male Canadian veterans.	Questionnaire and follow-up of death certificate.	6	124		*Cigarettes* NS .....1.00 <10 .....7.02(17) 10-20 ...13.05(49) >20 ....14.63(12) All .....11.42(78) *Pipes* SM .....2.11 (5) *Cigars* SM 3.57 (1)	*Cigarettes* NS .....1.00 <10 .....4.81 (9) 10-20 .....6.12(21) >20 .....6.93 (7) All .....5.85(37) *Pipes* SM .....0.75 (2) *Cigars* SM 3.33 (1)	
Hammond, 1966, U.S.A. (*103*).	440,568 males 562,671 females 35-84 years of age in 25 states.	Interviews by ACS volunteers.	4	389 SM .....369 NS 20			*Males* NS .....1.00 (20) SM (age 45-64) ..6.65(194) SM (age 65-79) .11.41(175)	
Kahn, 1966, U.S.A. (*132*).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	*Bronchitis* SM .....64 NS .....13 *Emphysema* SM .....284 NS 18	NS .....1.00 (31) All SM ...6.49(348) Current cigarettes .10.08(229) *Pipes* SM .....2.36 (9) *Cigars* SM 0.79 (5)	*Current cigarettes only* NS .....1.00(13) 1-9 .....3.63 (5) 10-20 ....4.51(22) 21-39 ....4.57(12) >39 .....8.31 (4) All .....4.49(43)	*Current cigarettes only* NS .....1.00 (18) 1-9 .....5.33 (10) 10-20 ....14.04 (93) 21-39 ....17.04 (62) >39 .....25.34 (17) All .....14.17(186)	

TABLE 1.—*Chronic obstructive bronchopulmonary disease mortality ratios* (*cont.*)

(Actual *number of deaths* shown *in parentheses*)[1]

SM *Smokers* NS *Nonsmokers*

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths	Cigarettes/day pipes, cigars	Chronic bronchitis	Emphysema	Other
PROSPECTIVE STUDY								
Weir and Dunn, 1970, U.S.A. (225).	68,153 males in various occupations in California.	Questionnaire and follow-up of death certificate.	5–8	58			*Cigarettes* NS .....[2]1.00 ±10 .....8.18 ±20 .....11.80 >30 .....20.86 All 12.33	
RETROSPECTIVE STUDY								
Wicken, 1966, Northern Ireland (227).	1,189 males.	Personal interview with relatives of individuals listed on death register.		1,188 obtained retrospectively. SM ....1,064 NS 124		*Cigarettes only* NS .....1.00(124) 1–10 .....2.95(245) 11–22 ....3.43(300) >23 .....4.44(168) *Mixed* SM .....1.55 (62) *Pipes or cigars* SM .....1.84(289)		

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

[2] NS includes pipe and cigar smokers; SM includes ex-smokers.

the findings for chronic bronchitis and emphysema. Such specific grouping of the mortality data should be viewed with some reservations in the light of the difficulties mentioned above in distinguishing the two diseases clinically.

The dose relationship of increased mortality ratios with increased consumption of cigarettes is indicated by the results of all the studies which present rates for different levels of smoking. Kahn (*132*), for instance, noted that those smoking only 1 to 9 cigarettes per day incurred an emphysema mortality ratio of 5.33 while those smoking over 39 per day incurred one of 25.34. Pipe and cigar smokers were found in some studies to have slightly elevated mortality ratios in comparison with nonsmokers although other studies did not show this. The risk of dying from COPD among cigar and pipe smokers appears to be much less than that incurred by cigarette smokers but may be somewhat greater than that among nonsmokers (table 1).

The effect of stopping smoking on COPD mortality is reflected in the results of Doll and Hill (*70, 71*) in their study of British physicians. They found that during the years immediately following cessation of smoking, mortality ratios remained elevated and did not begin to decline below the level of continuing smokers until nearly a decade later. This delay in response is probably due to two factors: the presence in the ex-smokers' group of many who quit for reasons of ill health and the long-term effects of cigarette smoke on the respiratory tree, some of which are irreversible. Kahn (*132*) also noted that the age-specific mortality ratios for ex-smokers were lower than those for continuing smokers of corresponding amounts of cigarettes.

A better estimate of the potential effect of stopping smoking on COPD mortality can be gained by studying the death rates in a population in which a high proportion of smokers have stopped smoking to protect their health rather than as a response to ill health. Among doctors age 35–64 in England and Wales, many of whom have stopped smoking cigarettes, there was a 24 percent reduction in bronchitis mortality between 1953–57 and 1961–65, as compared with a reduction of only 4 percent in all men of the same age in England and Wales, among whom there was no reduction of cigarette smoking. (*84*).

COPD Morbidity

Many investigators have studied the prevalence of bronchopulmonary symptoms (including those of chronic nonspecific respiratory disease) among smokers and nonsmokers. These studies are outlined in table A2. Their results indicate that the cigarette

smoker is much more likely to suffer from respiratory symptoms such as cough, sputum production, and dyspnea than is the nonsmoker. Such symptoms, particularly cough and sputum production, increase with increasing dosage of cigarette smoke. Table A2 also shows that pipe and cigar smokers experience COPD symptoms more frequently than nonsmokers although not to the degree found in cigarette smokers. These morbidity findings are similar to the mortality findings presented above.

Similarly, cessation of cigarette smoking has been shown to be associated with a decrease in symptom prevalence. Mitchell, et al. (*168*) studied 60 patients who succeeded in stopping smoking and 84 continuing smokers. Among the ex-smokers, more than 70 percent reported improvement in their cough while less than 5 percent of the continuing smokers did so. Wynder, et al. (*237*) followed 224 ex-smokers of cigarettes and noted that 77 percent reported cessation of persistent cough and an additional 17 percent reported definite improvement. Hammond (*102*) reported similar results concerning cough and shortness of breath in a study of a large group of ex-smokers.

Ventilatory Function

Another type of quantification of the effects of smoking on the bronchopulmonary system has been obtained by those groups of investigators who have studied pulmonary function in various groups. Results are presented in table A3, and a glossary of the terms used in the various tests is presented in table A4. The parameters investigated have included maximal breathing capacity (maximal voluntary ventilation), expiratory flow rates, forced expiratory volume, and vital capacity. Although certain of these parameters appear to be more sensitive measures of pulmonary dysfunction than others, the overwhelming majority of these studies have shown diminished function among smokers. An increase in the expected age-diminution rate in smokers has been observed in those studies which employed either repeated examinations or examinations at many different age levels. Higgins, et al. (*117*) conducted a nine-year follow-up examination of 385 male residents of a British industrial town who were age 55–64 at the beginning of the study. Among the survivors who were tested initially and nine years later, the average decline in $FEV_{0.75}$ was smallest in nonsmokers, slightly greater in ex-smokers, and greatest in smokers. As with COPD mortality and symptom prevalence, the impairment of pulmonary function shows a dose-relationship with increasing amounts of cigarettes smoked.

The data contained in table A3 provide two different kinds of information. The majority of the studies were conducted on unselected populations, which probably include a number of individuals with clinically manifest COPD. Therefore, these studies reflect the prevalence of COPD-related dysfunction (as determined by pulmonary function tests) in relation to smoking. However, some studies of younger individuals have revealed that pulmonary function tests are abnormal in clinically asymptomatic smokers.

Krumholz, et al. (*140*) and Rankin, et al. (*189*) have shown that pulmonary diffusing capacity is impaired in young asymptomatic smokers when compared with age-matched nonsmokers. Similar impairment in other pulmonary function tests was noted by Peters and Ferris (*182, 183*) in an asymptomatic college-age group and by Zwi, et al. (*241*) and Krumholz, et al. (*140, 142*) in groups of young asymptomatic physicians and medical students.

Several investigators have employed tests which measure the relationship of ventilation and perfusion (V/Q relationships) in the various pulmonary segments. These tests are predicated on observations that some segments of the lung may be relatively under or overperfused and that, likewise, segments may be under or overventilated. Anthonisen, et al. (*10*) investigated pulmonary function in 10 male smokers with clinically mild chronic bronchitis, all of whom had smoked cigarettes for at least 20 years. Regional pulmonary function was studied using radioactive xenon. Despite the fact that overall pulmonary function was nearly normal in several patients, all had depressed V/Q ratios in some lung regions with the basal areas being those most commonly affected. The authors suggested that significant disease in the peripheral airways may exist in patients whose chronic bronchitis is clinically mild and who show no present impairment of ventilatory capacity. The radioactive xenon test may reveal severe compromise of local gas exchange when usual studies of ventilatory capacity do not reveal any impairment. Similar results concerning peripheral airway obstruction in bronchitic patients with normal, or only minimally increased pulmonary resistance, have been observed by Woolcock, et al. (*234*). These authors also noted that their patients demonstrated frequency-dependent compliance which was unaffected by the administration of bronchodilator aerosols.

Strieder, et al. (*214*) have recently investigated the mechanism of postural hypoxemia in 24 asymptomatic smokers and nonsmokers. They found that standard ventilatory tests and lung volumes were normal in both the smoking and nonsmoking groups. However, the arterial pO_2 measured in the supine position was significantly lower among the smokers and alveolar-arterial oxygen gradients, while breathing room air, were larger in smokers than in

nonsmokers (more so in the supine than in the erect position). The increase in alveolar-arterial O_2 gradients was greater for heavy than for light smokers. The authors concluded that maldistribution of ventilation and perfusion accounted for the observed hypoxemia. They also felt that this mild diffuse airway disease among asymptomatic smokers is physiologically significant mainly because of involvement of small bronchi, as expressed by maldistribution unaccompanied by gross airway obstruction. A similar ventilatory distribution abnormality among smokers has also been observed by Ross, et al. (*198*) with the more severe alterations found in the long-term smokers.

Although of concern in the consideration of COPD, such disturbances of the V/Q relationship may also have adverse effects upon cardiac function depending upon the level of hypoxemia (*219*). The discussion in the section on Coronary Heart Disease noted that carbon monoxide has adverse effects on both oxygen transport and alveolar-arterial exchange as well as on oxygen debt developed with exercise (*50*). Further research is needed on the joint effect of these pulmonary and carbon monoxide induced hypoxemic influences.

A number of other studies have provided further evidence concerning the adverse effect of smoking on ventilatory function. Table 5 presents those experiments which deal with the effect of cessation of smoking on pulmonary function. Among the parameters which have been noted to improve after stopping smoking are: diffusing capacity, compliance, resistance, maximal breathing capacity, and forced expiratory volumes. These parameters showed improvement within 3 to 4 weeks after cessation of smoking.

Genetic Factors

Recent interest has been shown in the possible contribution of genetic factors to the pathogenesis of COPD. Earlier studies (*127, 147*) had noted the existence of kindreds with high incidences of chronic bronchitis, emphysema, or both diseases. In addition to the presence of genetic susceptibility, Larson, et al. (*147*) also observed that all but one of the 11 symptomatic individuals in their two kindreds were smokers. They postulated that the susceptibility of some smokers to develop emphysema may be, at least partially, genetically detemined.

More recently, Larson, et al. (*148*) studied 156 relatives of COPD patients and 86 control individuals. The subjects underwent pulmonary function testing, including forced expiratory volume and residual volume/total lung capacity measurements. The authors observed that pulmonary function abnormalities were most prevalent among the relatives who smoked and least prevalent among

TABLE 5.—*Cessation of smoking and human pulmonary function*[1]

Author, year, country, reference	Number and type of population	Results			Comments
Krumholz et al., 1965, U.S.A. (*141*).	10 physicians 25-33 years of age.	*Following 3 weeks abstinence* Lung volumes—no significant change. Peak expiratory flow rate—increase ($p<0.01$). Mean diffusing capacity: Resting—increase ($p<0.02$) Exercise—no change. Compliance—increased in 6/8 tested.	*Following 6 weeks abstinence (6 subjects only)*† Lung volumes: Inspiratory reserve volume—increase ($p<0.05$). Functional residual capacity—increase ($p<0.05$). Maximal breathing capacity—increase ($p<0.02$). Mean diffusing capacity—no change. Compliance—continued to show increase.		† All subjects were >5 pack per year smokers.
Wilhelmsen, 1967, U.S.A. (*230*).	16 smokers. (43.7 mean age).	*Value prior to cessation*	*Value after cessation*	*Significance*	Mean duration of the non smoking period was 40 days.
		Vital capacity 4.50	4.57	Not significant.	
		$FEV_{1.0}$ 3.38	3.52	$p<0.05$.	
		$FEV_{1.0}/FVC$ 75.0	76.8	Not significant.	
		PEFR 6.97	7.45	Not significant.	
		MEFR 50% 3.81	3.93	Not significant.	
		MEFR 25% 1.31	1.50	$p<0.05$.	
		Inspiratory resistance .2.07	1.43	$p<0.025$.	
		Expiratory resistance .2.80	2.04	$p<0.02$.	
		Compliance ..... No change			
Peterson et al., 1968, U.S.A. (*184*).	12 smokers studied at various intervals and compared with 12 continuing smokers.	*After 1 month cessation* MBC increase ($p<0.001$). $FEV_{1.0}$ increase ($p<0.01$).	*After 18 months cessation* Increase ($p<0.01$). Increase.		

[1] Abbreviations are explained in the glossary of bronchopulmonary table A4.