

TABLE A25.—*Experiments concerning the effect of smoking and nicotine upon blood lipids (cont.)*  
(Human Studies)

Author, year, country, reference	Number and type of population	Smoking procedure	Plasma free fatty acids	Serum cholesterol	Serum triglycerides	Other	Comments
Murchison and Fyfe, 1966, Scotland (139).	8 male and 4 female moderate smokers with various diseases 37-67 years of age.	2 cigarettes in 15 minutes. I. Lit-cigarettes. II. Unlit-cigarettes.	I. Definite increase. II. No change.	No change. No change.	No change. No change.		Both regular and sham smokers showed significant increases in concentration of serum oleic acid and significant decreases in concentration of serum palmitic acid.
Kershbaum et al., 1967, U.S.A. (105).	6 normal heavy cigarette smokers 28-45 years of age.	Various types of cigarettes of known nicotine content.	Regular cigarettes, filter cigarettes, charcoal-filter cigarettes, pipe tobacco plus cigarettes all showed similar increase in FFA. Lettuce leaf cigarettes had negligible effect.				Both catecholamine and nicotine excretion rates showed responses to the various cigarettes similar to that of the FFA response.

TABLE A25a.—*Experiments concerning the effect of smoking and nicotine upon blood lipids*  
(Animal Studies)

ANIMAL AND IN VITRO STUDIES							
Author, year, country, reference	Number and type of population	Smoking procedure	Plasma free fatty acids	Serum cholesterol	Serum triglycerides	Other	Comments
Wenzel and Beckloff, 1958, U.S.A. (206).	48 male New Zealand white rabbits.	I. Untreated control— 12 subjects. II. Regular diet plus 0.1 percent cholesterol— 12 subjects. III. Regular diet plus 2.28 mg./kg./day nicotine in water—12 subjects. IV. Diet plus— (a) 0.1 percent cholesterol (b) 2.28 mg./kg./day nicotine in water— 12 subjects.				Group II and IV showed an immediate increase in plasma cholesterol and phospholipids with a leveling with a leveling of response at 4 weeks. Group IV showed a further increase at 8-12 week period.	The authors consider an elevated cholesterol/ phospholipid ratio to be a notable indication of atherogenic susceptibility. The concomitant increase in phospholipids with the cholesterol may negate the importance of nicotine-induced hypercholesterolemia as an atherogenic stimulus.
Kershbaum et al., 1961, U.S.A. (194).	5 mongrel dogs.	Intravenous infusion of 20 mg./kg. nicotine in 20 minutes.	Definite increase in 13/15 observations.				
Kershbaum et al., 1965, U.S.A. (107).	20 adult mongrel dogs.	I. 9 received IM nicotine daily for 6 weeks; up to 1 mg./kg. II. 5 placebo injection. III. 6 control.	I. Significant increase in 8/9 dogs. II. No change. III. No change.		No change in any group.		

TABLE A25a.—*Experiments concerning the effect of smoking and nicotine upon blood lipids (cont.)*  
(Animal Studies)

ANIMAL AND IN VITRO STUDIES							
Author, year, country, reference	Number and type of population	Smoking procedure	Serum triglycerides	Plasma free fatty acids	Serum cholesterol	Other	Comments
Kershbaum et al., 1966, U.S.A. (108).	28 adult mongrel dogs.	Intravenous infusion of nicotine.		No change.			The authors report on the results of the use of nethalide (a Beta-adrenergic blocker), phenoxybenzamine, and chlorpromazine to block the FFA response to nicotine. Only nethalide was successful and this constitutes an indication that nicotine stimulates Beta-adrenergic receptors to release catecholamines which, in turn, stimulate the release of FFA.
Kershbaum et al., 1967, U.S.A. (110).	Sprague-Dawley rat fat-pad tissue.	Nicotine perfusion.					Although nicotine perfusion was not associated with FFA release from fat tissue, epinephrine did produce a significant increase in FFA release. The authors conclude that the sympathetic nervous system mediates the FFA response to nicotine in the intact animal.

TABLE A26.—Experiments concerning the effect of carbon monoxide exposure upon blood lipids

Author, year, country, reference	Number and type of population	Smoking procedure	Results
Kjeldsen and Damgaard 1968, Denmark (115).	8 male students 23-27 years of age.	Five daily one-half hour exposures to 0.5 percent CO for 8-10 days. Overall mean COHb result: .g was 12.5 percent.	No significant changes in total fatty acids, phospholipids, or triglycerides. Cholesterol showed a significant increase only during the last 3 days of exposure.
Kjeldsen, 1969, Denmark (113).	72 female albino rabbits: I. Regular diet, 24 subjects. II. Regular diet plus 2 percent cholesterol, 24 subjects. III. Regular diet plus 2 percent cholesterol, 24 subjects.	I. 12 control and 12 exposed to gradually increasing CO concentrations (0.015-0.40 percent) over a 4-week period. II. 12 control and 12 exposed to 0.020 percent CO for 35 days. III. 12 control and 12 exposed to 0.020 percent CO for 7 weeks, then 0.036 percent CO for 3 weeks.	I. Serum cholesterol concentrations rose quickly and then remained slightly above control values for the 4-week period. II. At 35 days, the serum cholesterol concentration in the exposed group was 2½ times that in the control group. III. Serum cholesterol concentrations among those exposed were significantly higher than those in the control group for 5 weeks of the 10-week period.
Kjeldsen, 1969, Denmark (113).	24 castrated male albino rabbits. Regular diet plus 2 percent cholesterol.	12 control and 12 maintained at 10 percent oxygen levels for 6 weeks, then 9 percent for 2 weeks.	Serum cholesterol and triglyceride concentrations rose to significantly higher levels during 3 of the 8 weeks. No changes noted in serum phospholipids.

TABLE A27.—*Smoking and thrombosis*

Author, year, country, reference	Number and type of population	Experimental conditions <sup>1</sup>	Whole blood clotting time	Pro-thrombin time	Partial thromboplastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Blackburn et al., 1959, U.S.A. (25).	16 adult schizophrenic patients, 8 university students, all smokers.	12 individuals smoked 2 high-nicotine standard brand cigarettes.									Plasma stypven time (-)	
Mustard and Murphy, 1963, U.S.A. (141).	7 white males with either CVD or COPD, all heavy smokers 35-72 years of age.	Compared after periods of abstinence or continuation of smoking.	(-)	(-)	(-)		(-)	(-)	(+) decrease	(+) increase	Platelet clumping time (±)	
Ambrus and Mink, 1964, U.S.A. (4).	20 healthy non-smoking medical students <30 years of age.	Deep inhalation of one nonfiltered cigarette.	(-)		(-)	(-)	(±) increase	(-)			Thromboplastin 2 generation time (-)	2 students became ill. Results reflect data on 18.
Ashby et al., 1965, Ireland (8).	27 male medical students and hospital staff members.	13 controls measured at 2 separate times 14 subjects measured before and after smoking 2 cigarettes in 20 minutes.					(+) increase					Increase of subjects greater than that of controls at $p < 0.01$ .

Author, year, country, reference	Number and type of population	Experimental conditions <sup>1</sup>	Whole blood clotting time	Pro-thrombin time	Partial thromboplastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Sogani and Joshi, 1965, India (174).	11 observations on male smokers all regular tobacco users.	Smoked 2 cigarettes or 2 biris or chewed 1 betel nut quid in 20 minutes.	(-)	(-)		(-)	(+) increase				Fibrinolysis (+) decrease	Bir-- tobacco wrapped in tobacco leaf.
Engelberg, 1965, U.S.A. (58).	40 male and 20 female hospital patients, all smokers 17-68 years of age.	2 cigarettes in 20 minutes.									Chandler (in vitro) thrombosis time + decrease	
Kedra and Korolko, 1965, Poland (100).	39 male and 11 female smokers and 24 male and 26 female nonsmokers 18-25 years of age.	5 cigarettes in 1 hour.	(±) decrease	(-)		(+) decrease					Thrombin time (±) decrease	
Murchison and Fyfe, 1966, Scotland (139).	8 males and 4 female patients with various diseases, all heavy smokers 37-67 years of age.	2 cigarettes in 15 minutes, lit or unlit cigarettes.					(+) (+) increase					† Smoking both lit and unlit cigarettes caused a rise in platelet adhesiveness which the authors correlated with rise in plasma non-esterified fatty acids.

TABLE A27.—*Smoking and thrombosis (cont.)*

Author, year, country, reference	Number and type of population	Experimental conditions <sup>1</sup>	Whole blood clotting time	Pro-thrombin time	Partial thrombo-plastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Glynn et al., 1966, Canada (71).	20 male and 17 female smokers and 9 male and 21 female nonsmokers 17-76 years of age.	3 cigarettes in 30 minutes.					(-)				Platelet serotonin (-) Platelet adenosine nucleotide (-)	Smokers found to have a greater tendency for platelet aggregation than non-smokers.
Engelberg and Futterman, 1967, U.S.A. (59).	94 male and 53 female patients and medical house staff.	1 cigarette in 5 minutes.									Thrombus formation time (+) decrease	No relation found with increase in free fatty acids.
Murphy, 1968, U.S.A. (149).	Literature review with summary of data and conclusions.						(±) increase	(±) increase	(+) decrease		Platelet adherence to vascular endothelium (+) increase Fibrinolysis (±) decrease Thrombus formation time (+) decrease	

Symbols:

— — No effect.

+ . . . Questionable effect.

+ = Definite effect.

<sup>1</sup> Results, unless otherwise stated, concern specific coagulation test as measured before and after smoking procedure noted.

TABLE A30.—*Experiments concerning the effect of nicotine and smoking upon the peripheral vascular system*

Author, year country, reference	
Moyer and Maddock, 1940, U.S.A. (134).	20 subjects (including heavy smokers) were studied for the effects of the following procedures on skin temperature: the inhalation of a lit cigarette, inhalation through an empty paper tube, or the administration of 1 mg. nicotine intravenously. All subjects responded with decreased cutaneous temperature following the smoking and nicotine procedures. No changes were noted following sham smoking.
Mulinos and Shulman, 1940, U.S.A. (138).	A number of experimental groups, each consisting of 6-17 persons, were studied for the effects of deep breathing and cigarette smoking on skin temperature and digit or limb plethysmography. The authors concluded that deep breathing alone could account for the changes in temperature and blood flow noted upon smoking and noted that denicotinized cigarettes evoked the same or greater vasoconstriction as that noted following the smoking of a standard cigarette.
Shepherd, 1951, Ireland (173).	50 young male smokers were studied with plethysmography before and after the normal and rapid inhalation of a standard cigarette. The author noted that rapid inhalation was associated with a prolonged decrease in extremity blood flow while a more natural rate of inhalation was followed by a momentary decrease in flow. The author considered the former reaction to represent the pharmacologic effect of the smoke and the latter to represent the physiologic response to deep breathing, as the natural inhalation of an unlit cigarette produced the same transient decrease in flow as did the natural inhalation of the lit cigarette.
Friedell, 1953, U.S.A. (70).	52 male and 48 female young smokers and nonsmokers were studied for the effects of smoking on hand blood volume as measured by the use of radioactive iodinated albumin. The inhalation of unfiltered cigarettes was associated with an average decrease in hand blood volume of 19 percent in men and 33 percent in women; while filtered cigarettes showed respective decreases of 11 percent and 21 percent.
Strömblad, 1959, Sweden (181).	11 male and female subjects (smokers and nonsmokers) were studied for the effect of the intra-arterial administration of nicotine (brachial artery) on blood flow to the hand as measured by venous occlusion plethysmography. Increasing doses of nicotine were associated with increasing numbers of individuals manifesting vasoconstriction. The vasoconstrictive effects of nicotine were abolished by the prior administration of either hexamethonium or pentolinium.
Barnett and Boake 1960 Australia (18).	9 male patients with intermittent claudication (7 were heavy smokers) were studied for the effect of smoking on blood flow to the leg as measured by venous occlusion plethysmography. Smoking an unfiltered cigarette was found not to produce any consistent changes in blood flow to the calf or foot of the affected leg.
Freund and Ward, 1960, U.S.A. (68).	15 male prison inmates (less than 35 years of age) and 14 male patients with peripheral vascular disease (approximately 65 years of age) were studied for the effect of smoking on digital circulation as measured by skin temperature, plethysmography, and radiosodium clearance from the skin. Smoking was found to adversely affect the first and third measures in a significant manner (while plethysmographic values were variable) only in the healthy prisoners and not at all in the patient group.
Roth and Schick, 1960, U.S.A. (161).	100 normal individuals underwent 425 experimental procedures concerning the effect of smoking on the peripheral circulation. Smoking was found to be associated with a decrease in extremity skin temperature.

TABLE A30.—*Experiments concerning the effect of nicotine and smoking upon the peripheral vascular system (cont.)*

Author, year, country, reference	
Rottenstein et al., 1960, U.S.A. (162).	8 males (18-31 years of age) were studied for the effect of intravenous nicotine on extremity temperature and blood flow. Intravenous nicotine was found to evoke a decrease in skin temperature while increasing muscle blood flow. The former effect began sooner and lasted longer than the latter.
Allison and Roth, 1969, U.S.A. (3).	30 healthy individuals (19-59 years of age) were studied for the effect of smoking two cigarettes on extremity pulse volumes and skin temperature. Smoking was found to be associated with a 2-6 percent decrease in skin temperature and a 45-50 percent decrease in blood pulse volumes to segments of the finger, calf, and toe.

## **CHAPTER 3**

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### **Chronic Obstructive Bronchopulmonary Disease**

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## 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

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\* 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)<sup>1</sup>  
 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	<i>Cigarettes</i>			
				NS . . . . . 30	NS . . . . . 1.00 (30)			
					<10 . . . . . 1.67 (10)			
					10-20 . . . . . 3.00 (57)			
					>20 . . . . . 3.64 (40)			
					All . . . . . 2.85 (231)			
					<i>Pipes</i>			
					NS . . . . . 1.00 (30)			
					SM . . . . . 1.77 (23)			
	<i>Cigars</i>							
	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				
					<i>Chronic bronchitis</i>			
					NS . . . . . 1.00			
					1-14 . . . . . 6.80			
					15-24 . . . . . 12.80			
					>25 . . . . . 21.20			
					All . . . . . 11.60			
					<i>Pipes and Cigars</i>			
					SM . . . . . 3.00			
						<i>Other</i>		
	NS . . . . . 1.00							
	1-14 . . . . . 0.65							
	15-24 . . . . . 1.08							
	>25 . . . . . 0.63							
	All . . . . . 0.81							
	<i>Pipes and Cigars</i>							
	SM . . . . . 0.78							

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

(Actual number of deaths shown in parentheses)<sup>1</sup>

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 (50).	Approximately 78,000 male Canadian veterans.	Questionnaire and follow-up of death certificate.	6	124		<i>Cigarettes</i>					
						NS	.....1.00	NS	.....1.00		
						<10	.....7.02(17)	<10	.....4.81 (9)		
						10-20	.....13.65(49)	10-20	.....6.12(21)		
						>20	.....14.63(12)	>20	.....6.93 (7)		
						All	.....11.42(78)	All	.....5.85(37)		
						<i>Pipes</i>					
						SM	.....2.11 (5)	SM	.....0.75 (2)		
						<i>Cigars</i>					
						SM	.....3.57 (1)	SM	.....3.33 (1)		
Hammond, 1966, U.S.A. (103).	440,558 males 562,671 females 35-84 years of age in 25 states.	Interviews by ACS volunteers.	4	389		<i>Males</i>					
						NS	.....1.00 (20)	SM (age			
								45-64)	..6.55(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			<i>Bronchitis</i>					
						NS	.....1.00 (31)	<i>Current ciga-</i>			
						SM	......64	<i>rettes only</i>			
						NS	......13	NS	.....1.00(13)	NS	.....1.00 (18)
								1-9	.....3.63 (5)	1-9	.....5.33 (10)
								10-20	.....4.51(22)	10-20	.....14.04 (93)
								21-39	.....4.57(12)	21-39	.....17.04 (62)
								>39	.....8.31 (4)	>39	.....25.34 (17)
								All	.....4.49(43)	All	.....14.17(186)

TABLE 1.—*Chronic obstructive bronchopulmonary disease mortality ratios (cont.)*  
 (Actual number of deaths shown in parentheses)<sup>1</sup>  
 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				
							<i>Cigarettes</i>	
							NS . . . . . <sup>2</sup> 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				
							<i>Cigarettes only</i>	
							NS . . . . .1.00 (124)	
							1-10 . . . . .2.95 (245)	
							11-22 . . . . .3.43 (300)	
							>23 . . . . .4.44 (168)	
							<i>Mixed</i>	
							SM . . . . .1.55 (62)	
							<i>Pipes or cigars</i>	
							SM . . . . .1.84 (289)	

<sup>1</sup> 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.

<sup>2</sup> 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 non-smoker. 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 non-smokers, 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<sub>2</sub> 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 determined.

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<sup>1</sup>

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.	<i>Following 3 weeks abstinence</i>		<i>Following 6 weeks abstinence (6 subjects only)†</i>	† All subjects were >5 pack per year smokers.	
		Lung volumes—no significant change.	Lung volumes:			Inspiratory reserve volume—increase (p<0.05).
		Peak expiratory flow rate—increase (p<0.01).		Functional residual capacity—increase (p<0.05).		
		Mean diffusing capacity:		Maximal breathing capacity—increase (p<0.02).		
		Resting—increase (p<0.02)		Mean diffusing capacity—no change.		
		Exercise—no change.				
		Compliance—increased in 6/8 tested.	Compliance—continued to show increase.			
Wilhelmsen, 1967, U.S.A. (230).	16 smokers. (43.7 mean age).	<i>Value prior to cessation</i>		<i>Value after cessation</i>	<i>Significance</i>	Mean duration of the non-smoking period was 40 days.
		Vital capacity	4.50	4.57	Not significant.	
		FEV <sub>1.0</sub>	3.38	3.52	p<0.05.	
		FEV <sub>1.0</sub> /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.	<i>After 1 month cessation</i>		<i>After 18 months cessation</i>		
		MBC increase (p<0.001).	FEV <sub>1.0</sub> increase (p<0.01).	Increase (p<0.01).	Increase.	

<sup>1</sup> Abbreviations are explained in the glossary of bronchopulmonary table A4.

the nonsmoking controls. No relationship of this increased prevalence could be demonstrated to alpha<sub>1</sub>-antitrypsin deficiency (see below). In addition, nonsmoking relatives and smoking controls were observed to show approximately the same prevalence of abnormalities. However, due to the large proportion of females in the nonsmoking relative group and to the clustering of two-thirds of the affected relatives in 10 families, firm conclusions cannot at present be drawn from this study concerning the relative contributions of smoking and of heredity to the pathogenesis of COPD.

In order to determine the relative significance of smoking and heredity in the pathogenesis of COPD, Cederlof, et al. (45, 46) have used the twin-study methods on registries in both Sweden and the USA. The specific details of this method are described in the section on Coronary Heart Disease. As may be noted from a summary of their work at the end of table A2, the authors compared the symptom prevalence among monozygotic and dizygotic twins who were both discordant and concordant for smoking habits. They observed that the hypermorbidity for COPD symptoms related to smoking persisted even after controlling for zygosity and concluded that a causal relationship of smoking and COPD symptoms was supported. However, genetic factors were still found to have an appreciable influence. Lundmann (159) has applied this method to the study of pulmonary function. He studied 37 monozygotic and 62 dizygotic twin pairs, measuring forced expiratory volumes and nitrogen washout gradients, and matched the various pairs for smoking discordancy. He observed that both of these parameters were adversely affected in twins who smoked and that these changes were correlated with cigarette consumption. The results are outlined at the end of table A3.

*Alpha<sub>1</sub>-antitrypsin (A<sub>1</sub>AT)*.—Of more recent note and discussion has been the discovery of an association between a hereditary predisposition to COPD and the relative or absolute absence of alpha<sub>1</sub>-antitrypsin, a serum glycoprotein enzyme. Eriksson (78) was the first investigator to observe a relationship between the presence of markedly decreased serum trypsin inhibitory capacity and panlobular emphysema. Since Eriksson's paper, much added research has been published concerning many facets of this intriguing area.

It appears that A<sub>1</sub>AT deficiency is inherited as an autosomal recessive trait (78, 216) although Kueppers (143) considers the transmission to be by an autosomal codominant allele. It has been estimated that up to 5 percent of the general population may be heterozygous for this gene (154) although full cross-sectional studies of the population remain to be done.

Homozygous or severe deficiency of this enzyme has been asso-