The Health Consequences of SMOKING

A Reference Edition

Selected Chapters From 1971 Through 1975 Reports
With Cumulative Index For All Reports
1964-1975

U.S. Department of Health, Education, and Welfare
Public Health Service
Center for Disease Control
Atlanta, Georgia 30333

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October 1977

Honorable Thomas P. O'Neill
Speaker of the House of Representatives
Washington, D.C. 20515

Dear Mr. Speaker:

As required by Section 8(a) of the Public Health Cigarette Smoking Act of 1969 (Public Law 91-222), enclosed is the 1976 Report to Congress on the Health Consequences of Smoking.

This year's report includes the "Bibliography on Smoking and Health - 1975," the official abstract bulletin of the National Clearinghouse for Smoking and Health, Bureau of Health Education, Center for Disease Control, Public Health Service. It presents the scientific information published since last year's report to Congress. Also part of this year's report is "The Health Consequences of Smoking, a Reference Edition," a compilation of selected chapters from previous reports to Congress. This reference edition was prepared to emphasize the fact that the major health risks from smoking are known and that recent scientific information refines the understanding of these relationships. Without doubt, cigarette smoking is a cause of cardiovascular disease, various types of cancer, and respiratory disease. Its toll in illness and premature death is needless and preventable.

Because of my strong commitment in reducing the morbidity and mortality which result from smoking, the Department is conducting a major review of its programs in this field in order to introduce administrative and legislative proposals to combat this problem.

Sincerely,

Joseph A. Califano, Jr.

Enclosure

PREFACE

ıe health consequences of cigarette smoking are well established
ıd have been clearly understood for several years. The causal re-
ţionships between cigarette smoking and an excess risk of devel-
ɔing cardiovascular disease, respiratory tract cancers, and chronic
ɒstructive lung disease, as well as the risk to the fetus, are well
ɒcumented and accepted by the scientific and health communities.

ɒr the past several years, new additions to the literature have
ıbstantiated these risks and further explained the mechanisms
ʏ which smoking produces disease, disability, and death; however,
ţsearch has identified no new major health risks. Therefore, it
ţems appropriate at this time to prepare a reference document
ţviewing the full range of health hazards due to smoking.

ţhis reference report consists of selected chapters from previous
ţports to the U.S. Congress which present summations of the
ʃown health hazards from smoking. Because the 1971 report was
ţreview of all information on smoking and health at that time,
ɒ chapters were included from reports prior to that time. This
ţference, coupled from the annual Bibliography on Smoking and
ţealth, represents a complete description of major smoking and
ţalth information.

ţe scientific evidence is clear and unavoidable, and the important
ţsk now is to convert this knowledge into programs for reducing
ıd eliminating the preventable death and disability related to the
ıoking habit.

Theodore Cooper, M.D.
Assistant Secretary for Health

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Previous Public Health Service Reports on Smoking and Health

Reviews of the scentific evidence linking smoking to health effects began in 1964 with Smoking and Health, Report of the Advisory Committee to the Surgeon General of the Public Health Service or as subsequently referred to "the Surgeon General's Report." After this report, Public Law 89-92 was passed requiring supplemental reports to Congress on this subject. In compliance, three reports were submitted:

1. The Health Consequences of Smoking, A Public Health Service Review: 1967.
2. The Health Consequences of Smoking, 1968 Supplement to the 1967 PHS Review.
3. The Health Consequences of Smoking, 1969 Supplement to the 1967 PHS Review.

In April 1970, Public Law 91-222 amended the previous law and called for an updated report on the health effects of smoking no later than January 1, 1971, with annual reports thereafter. The Health Consequences of Smoking, A Report of the Surgeon General: 1971, a comprehensive review of all the scientific literature available to the National Clearinghouse for Smoking and Health and with emphasis on the most recent additions to the literature was that updated report. Since then, the following annual reports on the health consequences of smoking have been submitted:

1. The Health Consequences of Smoking, A Report of the Surgeon General, 1972.
2. The Health Consequences of Smoking, 1973.
3. The Health Consequences of Smoking, 1974.
4. The Health Consequences of Smoking, 1975.

Each report since the original "Surgeon General's Report" has reviewed the scientific literature relevant to the association between smoking and

cardiovascular diseases, non-neoplastic bronchopulmonary diseases, and cancer. Smoking as related to the following diseases and conditions has been reviewed periodically in the reports:

Pregnancy (1967, 1969, 1971, 1972, 1973)

Peptic Ulcer Disease (1967, 1971, 1972, 1973)

Public Exposure to Air Pollution from Tobacco Smoke (1972, 1975)

Noncancerous Oral Disease (1969)

Tobacco Amblyopia (1971)

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Harmful Constituents of Cigarette Smoke (1972)

Exercise Performance (1973)

Pipe and Cigar Smoking (1973)

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Chapter 1

Overview – The Health Consequences of Smoking

Source:

1975 Report, Overview – The Health Consequences of Smoking, pages 1 - 8.

OVERVIEW – HEALTH CONSEQUENCES OF SMOKING

The statement, *"Warning: The Surgeon General Has Determined That Cigarette Smoking Is Dangerous to Your Health,"* has been required by law on cigarette packaging since 1970 as a part of the Public Health Cigarette Smoking Act of 1969. This Act was a response by the U.S. Congress to the scientific information on the health consequences of cigarette smoking summarized in reports then available (the Surgeon General's Report of 1964 and the subsequent 1967, 1968, and 1969 PHS Health Consequences of Smoking). This Act was passed because a series of important questions concerning cigarette smoking and health had been answered.

The following discussion summarizes the basic questions, the methodology used to determine the answers, and the answers themselves.

The initial question to be answered concerning the health consequences of smoking was *"Are there any harmful health effects of smoking cigarettes?"* The answer to this question was provided in two ways. First, it was demonstrated that some diseases occurred more frequently in smokers than in nonsmokers. Second, a causal relationship was established between smoking and these diseases.

Concern about the possible health effects of smoking started when scientists began looking for an explanation to account for the rapidly increasing death rate from lung cancer. The early retrospective studies showed a link between lung cancer and smoking. The first prospective studies, however, found that only one-eighth of the excess overall mortality found among smokers could be accounted for by lung cancer; the rest was largely due to coronary heart disease, chronic respiratory disease, and other forms of cancer. They also found that the effect on overall mortality was largely confined to cigarette smokers rather than the users of other forms of tobacco.

However, demonstrating an association by statistical probability is not enough to establish the causal nature of a relationship. Determining that the association between smoking and excess death rates is cause and effect was a judgment made after a number of criteria had been met, no one of which by itself is sufficient to make this judgment. These criteria as listed in the Surgeon General's

Advisory Committee Report (1964) were the consistency, strength, specificity, temporal relationship, and coherence of the association.

In addition, convincing theories about the mechanisms whereby smoking contributes to the various diseases responsible for the excess mortality among cigarette smokers were developed from the evidence on the biochemical, cytologic, pathologic, and pathophysiologic effects of cigarette smoking, thereby providing the necessary support for the decision that the relationship was causal.

The most important specific health consequence of cigarette smoking in terms of the number of people affected is the development of premature coronary heart disease (CHD). Both prospective and retrospective studies clearly established that cigarette smokers have a greater risk of death due to CHD and have a higher prevalence of CHD than nonsmokers. Long-term followup of healthy populations has confirmed that a cigarette smoker is more likely to have a myocardial infarction and to die from CHD than a nonsmoker. Cigarette smoking has been shown to be one of the major independent CHD risk factors and to act in combination with other major alterable CHD risk factors (high blood pressure and elevated serum cholesterol). Autopsy studies have shown that persons who smoked cigarettes have more severe coronary atherosclerosis than persons who did not smoke. Physiologic studies and animal experiments have indicated several mechanisms whereby these effects can take place.

A second major health consequence of smoking is the development of cancer in smokers. Cigarette smoking was firmly established as the major risk factor in lung cancer. The risk of developing lung cancer was found to be 10 times greater for cigarette smokers than for nonsmokers. The risk of developing lung cancer increases with the number of cigarettes smoked per day and is greater in cigarette smokers who report inhaling, who started smoking at an early age, or who have smoked for a greater number of years. Smokers of filter cigarettes have been shown to have a lower risk of developing lung cancer than smokers of nonfilter cigarettes, but the risk remains well above that for nonsmokers. The risk of developing cancer of the larynx, pharynx, oral cavity, esophagus, pancreas, and urinary bladder was also found to be significantly higher in cigarette smokers than in nonsmokers. Pipe and cigar smokers were found to have elevated risks for the development of cancer of the oral cavity, pharynx, larynx, and esophagus when compared to nonsmokers. Fewer pipe and cigar smokers than cigarette smokers report that they inhale. As a result lungs of pipe and cigar smokers receive much less

exposure to smoke than the lungs of cigarette smokers. This is probably the primary reason for the lower incidence of cancer of the lung for pipe and cigar smokers compared to cigarette smokers.

Women have had far lower rates of lung cancer than men. This has been attributed to the fact that fewer women than men smoke and the fact that women smokers generally select filter and low tar and nicotine cigarettes. However, the percentage of women smokers in the United States has increased steadily in the last 30 years, and since 1955 the death rates from lung cancer in women have increased proportionately more rapidly than the rates for men, reflecting this increased proportion of women smokers.

The tar from cigarette smoke has been found to induce malignant changes in the skin and respiratory tract of experimental animals, and a number of specific chemical compounds contained in cigarette smoke were established as potent carcinogens or co-carcinogens. Malignant changes including carcinoma *in situ* were found in the larynx and in the sputum exfoliative cytology of experimental animals exposed to cigarette smoke.

Nonmalignant respiratory disease is a third area of smoking-induced morbidity and mortality. Cigarette smokers have been shown to have more frequent minor respiratory infections, miss more days from work due to respiratory illness, and report symptoms of cough and sputum production more frequently than nonsmokers. Retrospective and prospective studies with long-term followup have found that cigarette smoking is the primary factor in the development of chronic bronchitis and emphysema in the United States. Cigarette smokers have also been found to be more likely to have abnormalities of pulmonary function and have higher death rates from respiratory diseases than nonsmokers. Data from autopsy studies have shown that cigarette smokers were more likely to have the macroscopic changes of emphysema, and that these changes are closely related to the number of cigarettes smoked per day. Mucous cell hyperplasia has been found more often in cigarette smokers. Cigarette smoke also inhibits the ciliary motion responsible for cleansing the respiratory tract.

An additional area of health concern has been the effect of cigarette smoking during pregnancy. Mothers who smoke cigarettes during the last two trimesters of their pregnancy have been found to have babies with a lower average birth weight than nonsmoking mothers. In addition cigarette smoking mothers had a higher risk of having a stillborn child, and their infants had higher late fetal and

neonatal death rates. There are some data to show that these risks due to cigarette smoking are even greater in women who have a high risk pregnancy for other reasons. These effects may occur because carbon monoxide passes freely across the placenta and is readily bound by fetal hemoglobin, thereby decreasing the oxygen carrying capacity of fetal blood.

Having established that cigarette smoking is a significant causal factor in a number of serious disease processes, two additional questions became important. They are *"Can the health consequences to the individual be averted by stopping smoking or by changing the cigarette,"* and *"What are the overall public health consequences of cessation and of the changes made in cigarettes?"*

The first question is the simpler of the two to answer. In the individual, cessation of cigarette smoking results in a rapid decline of the carbon monoxide level in the blood over the first 12 hours. Symptoms of cough, sputum production, and shortness of breath usually improve over the next few weeks. A woman who stops smoking by the fourth month of her pregnancy has no increased risk of stillbirth or perinatal death in her infant related to smoking. The deterioration in pulmonary function tests that occurs in some smokers becomes less rapid than that of continuing smokers. The death rates from ischemic heart disease, chronic bronchitis, and emphysema also become less than those of the continuing smoker. The risk of developing cancer of the lung, larynx, and oral cavity declines relative to the continuing smoker in the first few years after cessation and 10 to 15 years after stopping smoking approximates that of nonsmokers. A smoker who switches to filter cigarettes and has smoked them for 10 years or longer has a lower risk of developing lung cancer than a smoker who continues to smoke nonfilter cigarettes. The risk to a filter cigarette smoker, however, still remains well above that of a nonsmoker.

The public health benefits of cessation are more difficult to determine than the effects of cessation on the individual. Just as cause-specific death rates have reflected the effect of cigarette smoking on certain diseases, they should also reflect any substantial benefits to be gained by cessation or reduction in cigarette smoking. Several factors combined to produce a reduction in per capita dosage of tobacco exposure in the United States for the years 1966-1970. First, per capita consumption of cigarettes declined from 4,287 cigarettes per person in 1966 to 3,985 in 1970. Second, during this period there was a slow but significant decrease in the average tar and nicotine content of cigarettes as well as a decrease in the amount of

tobacco contained in the average cigarette. The decline in per capita consumption during those years occurred in the face of a substantial increase in the proportion of young women becoming smokers as compared to women of previous generations and so reflected predominantly a decrease in cigarette consumption by men.

Since 1970, although the per capita consumption of cigarettes has increased, the average levels of tar and nicotine have continued to decline, making it more difficult to predict what has happened to per capita dosage.

Examination of cause-specific death rates for the period of this declining per capita consumption reveals that there was a downturn in the male death rate from ischemic heart disease beginning in 1966 which reversed the upward trend that had occurred over the previous two decades. This decline in the death rate from ischemic heart disease has not occurred in women.

The male death rate from chronic bronchitis has also been declining since 1967, and the male death rate for emphysema has declined since 1968 when it was first recorded as a separate category. Female death rates for these two diseases have not shown these trends.

Despite the impressive coincidences of the decline in death rates among males occurring at the same time that there was a decline in per capita cigarette consumption, it is impossible to be certain of the exact cause of the decline in the death rates. These diseases are influenced by a variety of factors in addition to cigarette smoking such as blood pressure and air pollution. Some of these factors have also been subject to major control efforts which may have contributed to the decline in the death rates. In addition, there have been therapeutic advances in the treatment of these problems which may also have helped lower the death rates.

A decline in male death rates from lung cancer should also follow the decline in per capita consumption. This rate would not be influenced as much by changes in other etiologic factors or changes in therapy because cigarette smoking causes from 85 to 90 percent of all lung cancer and there have been no major improvments in survival due to changes in therapy. With lung cancer, however, two additional considerations must be kept in mind. A decline in death rates from lung cancer would be expected to lag several years behind a decline in per capita consumption. In addition, the decline in consumption and switch to low tar and nicotine cigarettes occurred

predominantly in the younger age groups where death rates from lung cancer are low. For these reasons, it is necessary to look at lung cancer death rates by age group rather than total lung cancer death rates. The lung cancer rates by age groups for 1971 suggest a decline in the lung cancer rates for the younger males (under 45), but the confidence limits on these trends at present remain wide enough that it is impossible to say whether this is a real decline or merely a leveling off. The national health statistics broken down by 5-year age groups are currently available only through 1971. The data by age group from a few more years will be necessary to determine whether the changes in smoking behavior which have taken place have reversed the trend of the preceding 40 years of continually increasing lung cancer rates in men. In 1971, the last year for which detailed mortality statistics are available, the accumulated exposure to cigarettes reached its peak among men born between 1915 and 1919, a group then in their early 50's. Cumulative exposure has continued to decline with each successive 5-year birth cohort born since then. The trends of the last few years offer some hope that the peak of the "lung cancer epidemic," as some have termed this phenomenon, may have been reached with this group and that future years will show a slow but consistent decline.

Chapter 2

Cardiovascular Diseases

Part I

Part II

Sources:

Part I — 1971 Report, Chapter 2, pages 15 - 174.
Part II — 1975 Report, Chapter 1, pages 9 - 38.

Chapter 2

Cardiovascular Diseases

Part I

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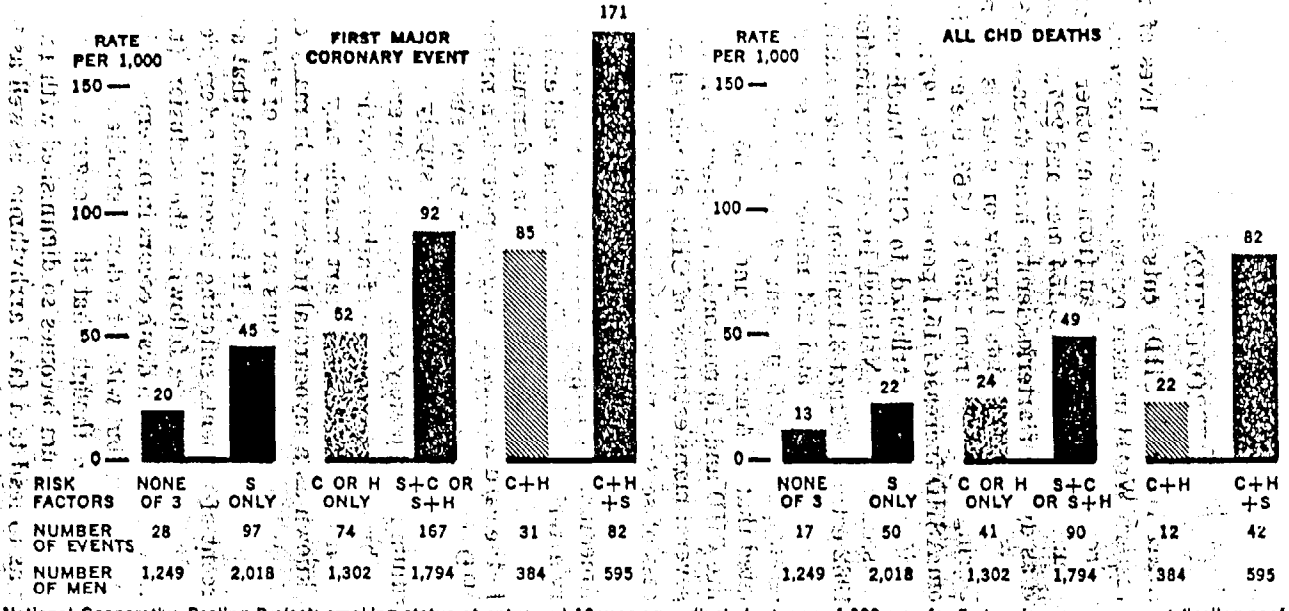
INTRODUCTION

Coronary Heart Disease (CHD) cuts short the lives of many men in the Western World in their prime productive years. More Americans die from heart disease than from any other disease. In 1967, in this country, a total of 345,154 men and 227,999 women were classified as dying of arteriosclerotic heart disease (ASHD) (*196*), a category which consists largely of what is commonly called CHD. During the years from 1950 to 1967, the age-adjusted death rate from ASHD increased 15.1 percent (*196, 197*).

Besides the many deaths attributed to CHD, much morbidity results from this disease. The National Health Examination Survey of 1960–1962 estimated that 3.1 million American adults, ages 18 to 79, had definite CHD and 2.4 million had suspect CHD, together representing about 5 percent of the population. It was further estimated that of Americans under age 65, almost 1.8 million had definite CHD and 1.6 million had suspect CHD (*195*).

There are several manifestations of CHD, all related in part to the basic process of severe atherosclerosis, a disease of arteries in which fatty materials (lipids) accumulate in the form of plaques in the walls of medium and large arteries. This process, as it occurs in the coronary arteries, leads to stiffening of the wall and narrowing of the lumen which, when severe, result in a diminution in the blood supply to the cardiac muscle. Angina pectoris, a major manifestation of CHD, results from diminution in blood supply relative to the needs of the myocardium. If the blood supply to a portion of the myocardium is completely obstructed, due for example to the formation of a thrombus at the site of atherosclerotic narrowing, necrosis or death of a portion of heart muscle may occur. This occurrence is known as a myocardial infarction. In many cases, a disturbance of cardiac rhythm occurs at the time of thrombosis, and the patient may die immediately. It is estimated that approximately 25 percent of patients suffering coronary artery occlusion die within the first three hours following the occlusion (table 1) (*88*). Not infrequently, sudden death occurs in patients with severe coronary atherosclerosis but without a demonstrable arterial occlusion. In these cases, it is thought that the meager blood flow to a portion of the myocardium becomes so diminished with respect to cardiac needs as to lead to a fatal arrhythmia, as well as to, perhaps, a myocardial infarction.

CIGARETTE SMOKING(S) AT ENTRY—WITH CONTROL OF SERUM CHOLESTEROL (C) AND DIASTOLIC BLOOD PRESSURE (H)—AND TEN YEAR INCIDENCE AND MORTALITY RATES. 7,594 WHITE MALES AGE 30–59 AT ENTRY, POOLING PROJECT



RISK FACTORS	NONE OF 3	S ONLY	C OR H ONLY	S+C OR S+H	C+H	C+H +S	NONE OF 3	S ONLY	C OR H ONLY	S+C OR S+H	C+H	C+H +S
NUMBER OF EVENTS	28	97	74	167	31	82	17	50	41	90	12	42
NUMBER OF MEN	1,249	2,018	1,302	1,794	384	595	1,249	2,018	1,302	1,794	384	595

National Cooperative Pooling Project; smoking status at entry and 10-year age-adjusted rates per 1,000 men for first major coronary event (incling nonfatal MI, fatal MI, and sudden death due to CHD) and any coronary death. U.S. white males age 30–59 at entry. All rates age-adjusted by 10-year age groups to the U.S. white male population 1960. Graphs present rates for noncigarette vs. cigarette smokers at entry with simultaneous control of blood pressure and serum cholesterol level. For this latter analysis, the following cutting points were used:

(a) Cigarette smoking S —any use at entry
(b) Serum cholesterol C — 250 mg./dl.
(c) Diastolic blood pressure H — 90 mm. Hg.

SOURCE: Inter-Society Commission for Heart Disease Resources. National Cooperative Pooling Project Data (88).

FIGURE 1—National Cooperative Pooling Project; smoking status at entry and 10-year age-adjusted rates per 1,000 men for first major coronary event (includes nonfatal MI, fatal MI, and sudden death due to CHD) and any coronary death. U.S. white males age 30–59 at entry. All rates age-adjusted by 10 year age groups to the U.S. white male population 1960. Graphs present rates for noncigarette vs. cigarette smokers at entry with simultaneous control of blood pressure and serum cholesterol level. For this latter analysis, the following cutting points were used:

(a) Cigarette smoking—S–any use at entry
(b) Serum cholesterol—C–≧250 mg./dl.
(c) Diastolic blood pressure—H–≧90 mm. Hg.

SOURCE: Inter-Society Commission for Heart Disease Resources. National Cooperative Pooling Project Data (*88*).

TABLE 1.—*Sudden death and acute mortality with first major coronary episodes*

Author, year, country, reference	Number and type of population	Data collection	Event	Number of events	Proportion per 1,000 events (as calculated on the basis of age-adjusted rates)	Comment
Pooling Project, American Heart Association, 1970, U.S.A. (*88*).	7,594 males males 30–59 years of age at entry. Ten-year experience.	Medical examination and follow-up.	All first major coronary episodes, nonfatal and fatal.	501	1,000.0	Data from the Pooling Project, Council on Epidemiology, American Heart Association, a national cooperative project for pooling data from the Albany civil servant, Chicago Peoples Gas Co., Chicago Western Electric Co., Framingham Community, Los Angeles civil servant, Minneapolis-St. Paul business men, and other prospective epidemiologic studies of adult cardiovascular disease in the United States.
			Sudden death (death within 3 hours of onset of acute illness)	123	245.5	
			All acute deaths with first episodes.	165	329.3	

SOURCE: Inter-Society Commission for Heart Disease Resources (*88*). Representative references include: (*54, 94, 148, 177*) and others listed as 6a–6k in Inter-Society Commission for Heart Disease Resources report.

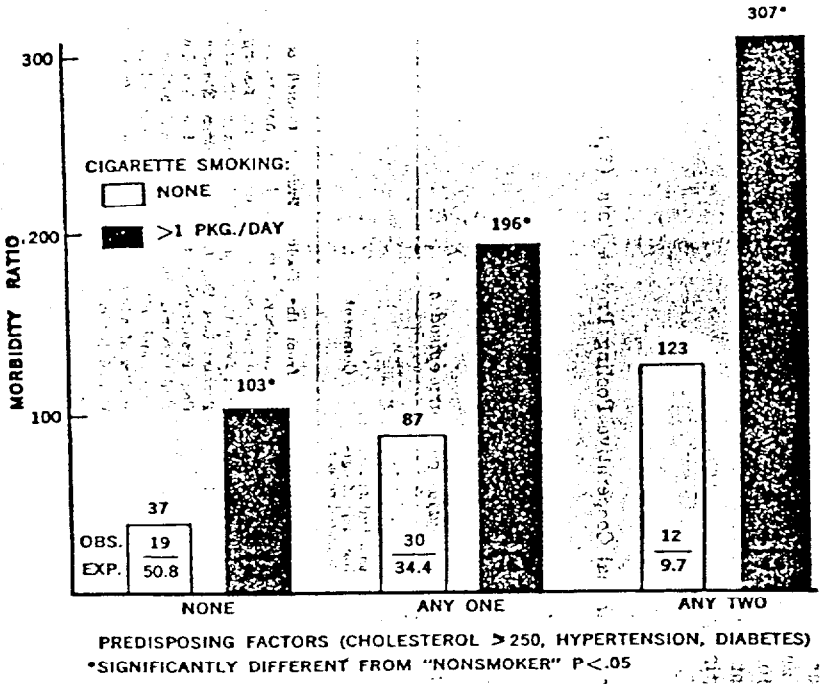


FIGURE 2—Risk of coronary heart disease (12 years) according to cigarette smoking habit and presence of "predisposing factors" (men 30–59 at entry). Framingham Heart Study.

SOURCE: Kannel, W. B., et al. (*94*).

Numerous epidemiological studies have indicated that cigarette smokers have increased mortality ratios for CHD; that is, cigarette smokers show significantly increased death rates compared with nonsmokers (table 2). The risk incurred by cigarette smoking increases with increasing dosage and, as measured by mortality ratios, is more marked for men in the younger age groups, under age 60, although the absolute increment in death rates experienced by smokers over that of nonsmokers continues to increase with increasing age. Table 2 lists the mortality ratios found in the major studies. Certain of these studies, including those at Framingham, Massachusetts, the Health Insurance Plan of New York City (HIP), and at Tecumseh, Michigan, have analyzed morbidity as well as mortality from CHD and have indicated that the risk of developing fatal and nonfatal CHD is greater among cigarette smokers than among nonsmokers (tables 3 and 4). Conflicting evidence has been published concerning the relationship of cigarette smoking and the incidence of angina pectoris. While some

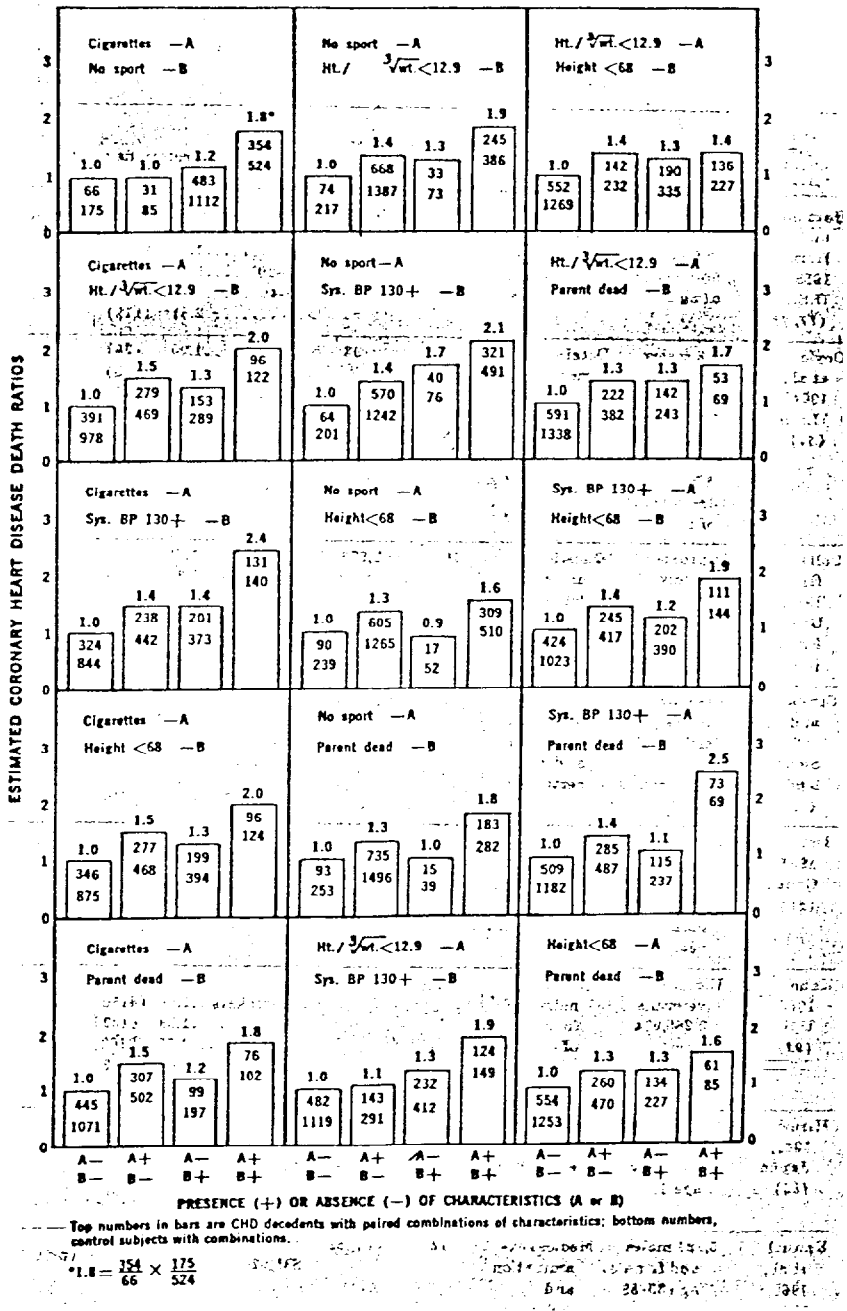


FIGURE 3—Estimated coronary heart disease death ratios in a 17–51 year follow-up, and frequencies of paired combinations of six high-risk characteristics in college, for all ages at death.

SOURCE: Paffenbarger, R. S., et al. (*146*).

TABLE 2.—*Coronary heart disease mortality*

(Actual number of deaths

[SM = Smokers

Author, year, country, reference	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day		
Hammond and Horn, 1958, U.S.A. (*77, 78*).	187,783 white males in 9 states 50–69 years of age.	Questionnaire and follow-up of death certificate.	3½	5,297	NS 1.00	(709)	[1](p<0.001)
					All smokers .1.70	(3361)	
					<10 .....1.29	(192)	
					10–20 ....1.89	(864)	
					20–40 ....2.20	(604)	
					>40 .....2.41	(118)	
Doyle et al., 1964, U.S.A. (*54*).	2,282 males, Framingham, 30–62 years of age.	Detailed medical examination and follow-up.	10	93	NS 1.00	(20)	
					All smokers .2.40	(73)	
					<20 .....2.00	(17)	
					20 .....1.70	(20)	
					>20 .....3.50	(36)	
	1,913 males, Albany, 39–55 years of age.		8				
Doll and Hill, 1964, Great Britain (*50*).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	1,376	NS 1.00		
					All smokers .1.35		
					1–14 ....1.29		
					15–24 ....1.27		
					>25 .....1.43		
Strobel and Gsell 1965 Switzerland (*180*).	3,749 male Swiss physicians.	Questionnaire and follow-up of death certificate.	9	162	NS 1.00		
					1–20 .....1.48		
					>20 .....1.76		
Best, 1966 Canada (*24*).	Approximately 78,000 male Canadian veterans.	Questionnaire and follow-up of death certificate.	6	2,000	NS 1.00		
					All smokers .1.60	(1380)	
					<10 .....1.55	(337)	
					10–20 .....1.58	(766)	
					>20 .....1.78	(277)	
Kahn 1966 U.S.A. (*93*).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	10,890	NS 1.00	(2997)	
					All smokers .1.74	(4150)	
					1–9 .....1.39	(439)	
					10–20 .....1.78	(2102)	
					21–39 .....1.84	(1292)	
					>39 .....2.00	(266)	
Hirayama, 1967, Japan (*84*).	265,118 Japanese adults over age 40.	Trained interviewers and follow-up of death certificate.	1	91	NS 1.00	(17)	
					1–24 .....1.13	(69)	
					>25 .....1.00	(5)	
Kannel et al., 1968, U.S.A. (*94*).	5,127 males and females age 30–59.	Medical examination and follow-up.	12	52	NS 1.00	(27)	(p<0.05)
					SM>20 ....2.20	(25)	

[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.

ratios related to smoking—prospective studies

shown in parentheses)[1]

NS = Nonsmokers]

Cigars, pipes	Age variation								Comments
Cigars		*50–54*		*55–59*		*60–64*		*65–69*	
NS..1.00	NS	1.00	(90)	1.00	(142)	1.00	(204)	1.00 (273)	
SM..1.28 (420)	All smokers	1.93	(765)	1.85	(962)	1.66	(921)	1.41 (718)	
Pipes	<10	1.38	(35)	1.38	(50)	1.17	(49)	1.27 (58)	
NS..1.00	10–20	2.00	(213)	2.04	(258)	1.91	(235)	1.58 (158)	
SM..1.03 (312)	>20	2.51	(203)	2.47	(199)	1.92	(129)	1.56 (78)	
									Data apply only to males aged 40–49 and free of CHD at entry. NS include pipe, cigar and ex-smokers.
		35–44		*45–64*		*65–84*			
	NS	1.00		1.00		1.00			
	1–14	3.73		1.40		1.71			
	15–24	4.45		1.73		1.27			
	>25	1.36		1.92		1.58			
NS..1.00									
SM..1.45									
Cigars		*30–49*		*50–69*		*70 and over*			
NS..1.00	NS	1.00		1.00		1.00			
SM..0.98 (16)	<10	0.97	(18)	1.56	(220)	1.71	(99)		
Pipes	10–20	1.45	(115)	1.67	(557)	1.29	(94)		
NS..1.00	>20	1.85	(65)	1.76	(184)	1.73	(28)		
SM..0.96 (95)									
Cigars									
NS..1.00									
SM..1.04 (623)									
Pipes									
NS..1.00									
SM..1.08 (886)									
									Preliminary report.

[1] "p" values specified only for those provided by authors.

TABLE 2.—*Coronary heart disease mortality ratios*

(Actual number of deaths

{SM = Smokers

Author, year, country, reference	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day	Males	Females	
Hammond and Garfinkel, 1969, U.S.A. (*76*).	358,534 males 445,875 females age 40–79 at entry.	Questionnaire and follow-up of death certificate.	6	14,819		*Males*	*Females*	
					NS	1.00	1.00	
					1–9	1.27	0.84	
					10–19	1.60	1.22	
					20–30	1.78	1.52	
					>40	1.77	0.61	
Paffenbarger and Wing 1969 U.S.A. (*146*)	50,000 male former students.	Baseline interview and examination and follow-up by death certificate.	17–51	1,146 matched with 2,292 controls	NS SM	1.00 1.50	(385)	($p<0.01$)
Paffenbarger et al., 1970, U.S.A. (*144*).	3,263 male longshoremen 35–64 years of age.	Initial multiphasic screening and follow-up of death certificate.	16	291	NS and <20 SM >20	1.00 2.08	(137) (154)	($p<0.01$)
Taylor et al., 1970, U.S.A. (*185*).	2,571 male railroad employees 40–59 years of age at entry.	Interviews and regular follow-up examination.	5	46	NS <20 >20	1.00 1.97 3.60	(4) (20) (22)	
Weir and Dunn, 1970, U.S.A. (*205*).	68,158 California male workers 35–64 years of age at entry.	Questionnaire and follow-up of death certificate.	5–8	1,718	NS All smokers ±10 ±20 >30	1.00 1.60 1.39 1.67 1.74		
Pooling Project, American Heart Association, 1970, U.S.A. (*88*).	7,427 white males 30–59 years of age at entry.	Medical examination and follow-up.	10	289	NS <10 20 >20	1.00 1.65 1.70 3.00	(27) (84) (86) (68)	

[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.

related to smoking—prospective studies (cont.)

shown in parentheses)[1]

NS = Nonsmokers]

Cigars, pipes	Age variation				Comments
		Males			†Based on
	40–49	*50–59*	*60–69*	*70–79*	5–9 deaths.
NS	1.00	1.00	1.00	1.00	
1–9	1.60	1.59	1.48	1.14	
10–19	2.59	2.13	1.82	1.41	
20–30	3.76	2.40	1.91	1.49	
>40	5.51	2.79	1.79	1.47	
		Females			
NS	1.00	1.00	1.00	1.00	
1–9	1.81	1.15	1.04	0.76	
10–19	2.08	2.37	1.79	0.98	
20–30	3.62	2.68	2.08	1.27	
>40	†3.31	3.73	†2.02	—	

	30–44	*45–54*	*55–69*	
NS	1.00	1.00	1.00	
	($p<0.01$)			
SM	1.80 (88)	1.60 (163)	1.20 (134)	

Data apply only to those free of CHD at entry.

	35–44	*45–54*	*55–64*	*65–89*	NS includes
NS	1.00	1.00	1.00	1.00	pipes and
±10	4.22	2.05	1.41	1.17	cigars.
±20	6.14	3.17	1.64	1.26	SM includes
±30	8.57	3.83	1.66	1.36	ex-smokers.
>40	7.93	3.15	1.42	1.42	
All	6.24	2.95	1.56	1.24	

1.00 (27)
1.20 (24)

TABLE 3.—*Sudden death from coronary*

(Mortality ratios—actual number

Author year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths
Pooling Project, American Heart Association, 1970, U.S.A. (*88*).	7,427 white males 30–59 years of age at entry.	Medical examination and follow-up.	10	145

TABLE 4.—*Coronary heart disease*

(Risk ratios—actual number of CHD

[SM = Smokers NS = Nonsmokers

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day
Doyle et al., 1964, U.S.A. (*54*).	2,282 males Framingham, 30–62 years of age. 1,913 males Albany, 39–55 years of age.	Detailed medical examination and follow-up.	10	243 myocardial infarctions and CHD deaths.	NS .....1.00 (52) All smokers ....2.36 (191) <20 .....1.98 (44) 20 .....2.05 (64) >20 .....3.04 (83)
Stamler et al., 1966, U.S.A. (*177*).	1,329 CHD-free male employees of Peoples Gas Company 40–59 years of age.	Interview and examination with clinic follow-up.	4	46 CHD	NS .....1.00 (2) <10 cigarettes, < 5 cigars, < 5 pipes .....2.92 (6) 10–19 cigarettes.3.67 (8) >20 cigarettes, > 5 cigars, > 5 pipes 3.83 (29)
Epstein, 1967, U.S.A. (*61*).	6,565 male and female residents of Tecumseh, Mich.	Initial medical examination and repeat follow-up examinations.	4	96 male, 92 female CHD including deaths, angina, and myocardial infarctions.	*Males 40–59* NS .....1.00 (1) EX .....6.53 (10) Cigarettes .....5.20 (36) *Females* NS .....1.00 (21) EX .....0.89 (3) Cigarettes 1.02 (14)

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

heart disease related to smoking

of deaths shown in parentheses)

Cigarettes/day	Cigars, pipes	Comment
Never smoked 1.00 (15)	1.00 (15)	See table 1 for description of Pooling Project.
≦10 .....1.90 (23)	1.86 (13)	
20 .....1.90 (50)		
>20 .....3.36 (44)		

morbidity as related to smoking

manifestations shown in parentheses)[1]

EX = Ex-smokers]

PROSPECTIVE STUDIES—Continued

Pipes, cigars	Age variation	Comments
		Data include CHD deaths, only on males 40–49 years of age and free of CHD on entry. NS includes pipes, cigars, and ex-smokers.
		NS includes ex-smokers. Includes all CHD.
Males—Continued *60 and over* 1.00 (7) SM 1.27 (11) 1.96 (23) SM *Females*—Continued 1.00 (47) 1.31 (5) 0.42 (2)	*Males* *40–59* ....1.80 (2) *60 and over* 0.86 (6)	Reexamination of patients was spread over 1½–6-year period, but data are reported in terms of 4-year incidence rates. Actual number of CHD incidents derived from data on incidence and total in smoking class.

TABLE 4.—*Coronary heart disease*

(Risk ratios—actual number of CHD
(SM = Smokers NS = Nonsmokers

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day
Jenkins, et al., 1968, U.S.A. (*90*).	3,182 males 39–59 years of age at entry.	Initial medical examination and follow-up by repeat examinations.	4½	104 myocardial infarctions.	NS .....1.00 (21) EX .....2.47 (15) Current .....2.78 (68) 0–15/day .....†1.39 (45) >16 .....3.06 (59)
Kannel, et al., 1968, U.S.A. (*94*).	5,127 males and females 30–59 years of age.	Medical examination and follow-up.	12	228 myocardial infarctions. 380 CHD.	*Myocardial Infarction* *Males* NS .....1.00 (21) All SM .....1.51 (153) Heavy SM ....1.85 (59) *Risk of CHD (overall)* *Males* NS .....1.00 (61) 1–10 .....1.34 (25) 11–20 .....1.80 (90) >20 .....2.41 (76)
Shapiro et al., 1969, U.S.A. (*172*).	110,000 male and female enrollees of Health Insurance Plan of Greater New York (HIP) 35–64 years of age.	Baseline medical interview and examination and regular follow-up.	8	Total unspecified.	*Males* NS .....1.00 All current ....2.14 cigarettes ($p<0.01$) <20 .....1.50 >20 .....2.33 >40 .....6.36
Keys 1970 Yugoslavia Finland Italy Netherlands Greece (*111*).	9,186 males in 5 countries 40–59 years of age at entry.	Interviews and regular follow-up examination by local physicians.	5	65 deaths. 80 myocardial infarctions. 128 angina pectoris. 155 other †428 total.	NS, EX (SM <20) ...1.00 (305) All current (>20) 1.31 (103)

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

morbidity as related to smoking (cont.)

manifestations shown in parentheses)[1]
EX = Ex-smokers]

PROSPECTIVE STUDIES—Continued

	Pipes, cigars	Age variation			Comments
			39–49	*50–59*	†Includes non-smokers and ex-smokers.
(p<0.001)		NS.....	1.00 (4)	1.00 (6)	
(p<0.001) (comparing 0–15 and 16+)		Current	4.23 (35)	2.26 (33)	NS includes former pipe and cigar smokers.

Myocardial infarction—Continued								
Females								
1.00 (31)								
1.71 (23)								
Risk of CHD (overall)—Continued								
Females								
1.00 (89)								
0.86 (18)								
1.29 (18)								
0.93 (3)								
Females	*Males only*	*Males*			*Females*			Total myocardial infarction includes those dead within *48 hours*.
		35–44	*45–54*	*55–64*	*35–44*	*45–54*	*55–64*	
1.00	NS 1.00	1.00	1.00	1.00	1.00	1.00	1.00	
2.00	SM 1.82	2.47	3.06	1.69	2.25	2.87	1.80	
(p>0.01)	(p<0.01)	0.52	2.16	1.32				
1.77		3.04	3.29	1.81	1.25	2.81	1.65	
5.92		10.09	7.69	5.80	20.25	11.79	4.07	
								NS include ex-smokers.

Includes all CHD incidence including EKG diagnoses.
Covers all countries investigated except U.S.A.
† Difference between total CHD and the sum of smoking *groups is due* to difference in figures presented by authors.

TABLE 4.—*Coronary heart disease*

(Risk ratios—actual number of CHD
[SM = Smokers NS = Nonsmokers

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day
Taylor, et al. 1970 U.S.A. (*183*).	2,571 male railroad employees 40–69 years of age at entry.	Interviews and regular follow-up examination.	6	46 deaths. 33 myocardial-infarctions. 78 angina pectoris. 55 other CHD. 212 total.	NS and EX ....1.00 (62) All current 1.77 (150)
Dayton et al., 1970, U.S.A. (*48, 49*).	422 male U.S. veterans participating as controls in a clinical trial of a diet high in unsaturated fat.	Interviews and routine follow-up examinations.	up to 8	27 sudden deaths. 44 definite myocardial infarctions.	<10 .....1.00 (26) 10–20 .....1.04 (22) >20 .....1.17 (13)
Dunn et al., 1970 U.S.A. (*55*).	13,148 male patients in periodic health examination clinics.	Data only on new incidents extracted from clinic records.	up to 14	Total unspecified.	
Pooling Project, American Heart Association 1970, U.S.A. (*88*).	7,427 white males 30–59 years of age at entry.	Medical examination and follow-up.	10	538 Includes fatal and nonfatal myocardial infarction and sudden death.	Never smoked ..1.00 (53) <10 .....1.65 (72) 20 .....2.08 (205) >20 .....3.28 (154)
Paul et al., 1963, U.S.A. (*148*).	1,989 Western Electric Co. male workers participating in a prospective study for 4½ years.	Screening examination and history.			*Coronary cases (87)* NS ..... 23 1–7 ..... 2 8–12 ..... 9 13–17 ..... 6 18–22 ..... 47 23–27 ..... 3 >28 9

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

morbidity as related to smoking (cont.)

manifestations shown in parentheses)[1]
EX = Ex-smokers]

PROSPECTIVE STUDIES—Continued

Pipes, cigars	Age variation	Comments
		All CHD including EKG diagnoses.
		No data on NS as a separate group.
	30–39 *40–49* *50–59* †Low SM 1.00(25) 1.00(125) 1.00(157) ‡High SM 2.17(10) 0.90 (31) 1.41 (53)	† Includes NS, EX, and <20 cigarettes/day. ‡ >20 cigarettes/day.
		Includes all CHD but *excludes death.*
		No data available comparing smokers and nonsmokers.
1.00(53) 1.25(54)		
		88 developed clinical coronary disease, 47 angina pectoris, 28 myocardial infarction, 13 deaths CHD.
Noncoronary controls ***(1,788)***		
33		
7		
11		
12		
30		
2		
6		
(p<0.005)		

studies have shown an increased risk of this manifestation among smokers, others have not (see table 5).

From these longitudinal studies, it has become increasingly clear that cigarette smoking is one of several risk factors for CHD and that it exerts both an independent effect and an effect in conjunction with the other risk factors. The basic concept may be expressed as follows: The more risk factors a given individual has, the greater the chance of his developing CHD. The importance of the constellation of coronary risk factors which include cigarette smoking, high blood pressure, and high serum cholesterol in predicting the risk for CHD is illustrated in figures 1 through 3. Other risk factors are included in certain of these figures and are discussed below.

Knowledge of the effects of cigarette smoke on the cardiovascular system has developed concurrently with the knowledge derived from the epidemiological studies. Nicotine, as well as cigarette smoke, has been shown to increase heart rate, stroke volume, and blood pressure, all most probably secondary to the promotion of catecholamine release from the adrenal gland and other chromaffin tissue. This release of catecholamines is also considered to be the cause of the rise in serum free fatty acids observed upon the inhalation of cigarette smoke. Studies concerning the effect of nicotine on cardiac rhythm have also suggested that smoking might contribute to sudden death from ventricular fibrillation.

In addition, research efforts have also been directed toward the effects of smoking on blood clotting and thrombosis; since many cases of sudden death and myocardial infarction are associated with thrombosis in a diseased coronary artery branch. Cigarette smoking may be associated with increased platelet aggregation *in vitro* and thus might play a role in the development of such thrombi or platelet plugs *in vivo*.

Other mechanisms have been investigated. Because cigarette smoking has been shown in some studies to be related to the prevalence of angina pectoris as well as to the incidence of myocardial infarction, it has been suggested that smoking enhances the development of atherosclerotic lesions. Autopsy and experimental studies have shown that cigarette smoking plays a role in atherogenesis. The administration of nicotine has been observed to increase the severity of cholesterol-induced atherosclerotic lesions in experimental animals. Attention is presently being given to carbon monoxide, which is present in cigarette smoke in such concentrations as to cause carboxyhemoglobin concentrations in the blood of smokers as high as 10 percent. Based on research in animals, it is reasonable to conclude that the atherosclerotic process may be enhanced, in part, by the relative arterial hypoxemia in cigarette

TABLE 5.—*Coronary heart disease morbidity as related to smoking—angina pectoris—prospective studies*

(Risk ratios—actual number of CHD manifestations shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day	Cigars and pipes	Age variation	Comments
Doyle et al., 1964, U.S.A. (54).	2,282 males, Framingham, 30–62 years of age.	Detailed medical examination and follow-up.	10	81	NS .....1.00(80) All .....1.09(51) <20 .....1.17(15) 20 .....0.99(18) >20 .....1.15(18)			NS include ex-smokers and pipe and cigar smokers.
	1,918 males, Albany, 39–56 years of age.		8					
Jenkins et al., 1968, U.S.A. (90).	3,182 males aged 39–59 at entry.	Initial medical examination and follow-up by repeat examination.	4½	29	NS .....1.00 (9) All current cigarettes .....1.44(16) >16 .....1.63(14)			NS include former pipe and cigar smokers.
Kannel et al., U.S.A. (94).	5,127 males and females years of age 30–59	Medical examination and follow-up.	12	107	*Males* NS .....1.00(16) Heavy SM, >20 cigarettes .....2.04(17) *Females* NS .....1.00(58) Cigarette SM .....0.65(16)			
Shapiro et al., 1969, U.S.A. (173).	110,000 male and female enrollees of New York City HIP 35–64 years of age.	Baseline medical interview and examination and regular follow-up.	8	Total Unspecified	*Males* *Females* NS .....1.00 1.00 Current cigarettes †1.91 1.20 <40 .....1.51 1.20 >40 .....4.85	*Males* NS...1.00 SM..‡1.71	*Males* *35–44* *45–54* *55–64* NS .....1.00 1.00 1.00 Current cigarettes ..3.40 1.57 2.06 <40 .....2.35 1.40 1.54 >40 .....10.15 2.58 6.15 *Females* NS .....1.00 1.00 1.00 Current cigarettes ..1.58 1.67 0.97 <40 .....1.67 1.58 1.04 >40 ..... — 4.12 —	†($p<0.01$) ‡($p<0.05$) NS include ex-smokers.

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

smokers caused by the increased carboxyhemoglobin level.

With respect to the acute event of myocardial infarction, attention has been focused on the role of nicotine. Nicotine stimulates the myocardium, increasing its oxygen demand. Other experiments have demonstrated that in the face of diminished coronary flow (due to partial occlusion from severe atherosclerosis in man or to partial mechanical obstruction in the animal), nicotine does not lead to an increase in coronary blood flow as seen in the normal individual. These effects exaggerate the oxygen deficit when the supply of oxygen has already been decreased by the presence of carboxyhemoglobin. Thus, a marked imbalance between oxygen demand (which has been increased) and oxygen supply (which has been decreased) is created by the inhalation of CO and nicotine. This imbalance may contribute to acute coronary insufficiency and myocardial infarction.

EPIDEMIOLOGICAL STUDIES

Numerous epidemiological studies, both retrospective and prospective, have been carried out in various countries in order to identify the risk factors associated with the development of coronary heart disease (CHD). Many of these studies have included smoking as one of the variables investigated. Tables 2 to 4 present the major findings.

Coronary Heart Disease Mortality

Table 2 lists the various prospective studies concerning the relation of CHD mortality and smoking. These studies demonstrate the dose-related effect of cigarette smoking on the risk of developing CHD. For example, the Dorn Study of U.S. Veterans as reported by Kahn (*93*) reveals progressively increasing mortality ratios, from 1.39 for those smoking 1 to 9 cigarettes per day to 2.00 for those smoking more than 39 cigarettes per day. Although the data are not detailed in the accompanying tables, several of these studies have also shown that increased rates of CHD mortality are associated with increased cigarette dosage, as measured by the degree of inhalation and the age at which smoking began. Although not as striking, the data for females reveal the same trends.

In most studies, the smokers' increased risk of dying from CHD appears to be limited mainly to those who smoke cigarettes. Some studies that have investigated other forms of smoking have shown much smaller increases in risk for pipe and cigar smokers when compared to nonsmokers. However, the recent study by Shapiro, et al. (*172*) of a large population enrolled in the Health Insurance Plan (HIP) of New York City showed a significantly increased

risk for the development of myocardial infarction and rapidly fatal myocardial infarction for a group consisting of both pipe and cigar smokers.

Table 3 details the findings of the American Heart Association Pooling Project on sudden death. The Pooling Project, a national cooperative project of the AHA Council on Epidemiology, is described in table 1 (*88*). Cigarette smokers in the 30 to 59 year age group incurred a risk of sudden death from CHD substantially greater than that of nonsmokers. Pipe and cigar smokers were observed to show a risk slightly greater than that of nonsmokers (table 3).

The relative risk of CHD mortality is greatest among cigarette smokers (as well as among those with other risk factors) in the younger age groups and decreases among the elderly. In table 2, Hammond and Horn found that for those smoking more than one pack per day, the risk is 2.51 in the 50 to 54 year age group and 1.56 in the 65 to 69 year age group. Although the relative risk for CHD among smokers decreases in the older age groups, the actual number of excess deaths among smokers continues to climb since the differences in death rates between smokers and nonsmokers continue to rise.

Coronary Heart Disease Morbidity

Tables 4 and 5 list the prospective studies carried on in a number of countries to identify the risk of CHD morbidity incurred by smoking. Here, CHD morbidity includes myocardial infarction as well as angina pectoris. Certain studies, notably those of Doyle, et al. (*54*), Keys, et al. (*111*), and Taylor, et al. (*183*) include a number of CHD deaths in their data that could not be separated out using the information provided in their respective reports. As noted in the discussion on CHD mortality, the CHD risk ratio increases significantly as the number of cigarettes smoked per day increases. Similarly, the HIP data of Shapiro, et al. (*172*) show that the elevated morbidity ratios declined with increasing age as has been shown for mortality ratios.

A recent monograph edited by Keys (*111*) dealt with the 5-year CHD incidence in males age 40 to 59 from seven countries. As summarized in table 4, cigarette smoking was found to be associated with an increased incidence of CHD in the U.S. railroad worker population, 2,571 individuals (*183*). None of the differences in ratio between smokers and nonsmokers was statistically significant for the 13 other population samples which varied in size from 505 to 982 individuals, from the five other countries. (Smoking was not considered in the two Japanese populations.) When more cases

become available to provide greater statistical stability to the rates, this intercultural comparison should prove illuminating.

The results of those studies which have separated out angina pectoris as a manifestation of CHD are presented in table 5. Doyle, et al. (*54*) found no relationship between this manifestation of CHD and cigarette smoking. Both Jenkins, et al. (*90*) and Kannel, et al. (*94*) observed increased risk ratios among male cigarette smokers although these differences were not statistically significant. More recently, Shapiro, et al. (*172*) found a significantly increased risk for angina among their male cigarette smokers as well as increasing risk ratios with increasing dosage among both males and females, particularly in the younger age groups. A variety of hypothetical explanations have been advanced to account for this seeming contradiction. Among these are the relatively small number of cases, the difficulties associated with the definitive diagnosis of the syndrome, and differences in the methods of classifying those cases of angina pectoris which are followed by myocardial infarction.

Retrospective Studies

Table A 6 presents data from the various retrospective studies of CHD prevalence. Most of these are case-control studies and show an increased percentage of smokers among those with clinical CHD when compared with a selected control population, usually without apparent CHD. Two of these studies include data on mortality.

The Interaction of Cigarette Smoking and Other CHD Risk Factors

The preceding section has reviewed the epidemiologic evidence which supports the judgment that cigarette smoking is a significant risk factor in the development of CHD. Many of the studies discussed above have identified a number of biochemical, physiological, and environmental factors, other than cigarette smoking, which also increase the risk of developing CHD. These risk factors include elevated serum lipids (particularly serum cholesterol) and hypertension, which, with cigarette smoking, are considered to be of greatest importance. Other factors are obesity, physical inactivity, elevated resting heart rate, diabetes (as well as asymptomatic hyperglycemia), electrocardiographic abnormalities, and a positive family history of premature CHD (*88*).

A number of these studies have also found that these factors, when present in the same individual, exert a combined effect on the risk of developing CHD. Figures 1 through 3 depict this interaction of risk factors. As may be noted in Figures 1 and 2, the

additional factor of smoking greatly increases the risk of developing CHD among those people already at high risk because of other factors.

Furthermore, these studies have shown that the effect of smoking on the risk of developing CHD is statistically independent of the other risk factors. That is, when the effect of the other factors is statistically controlled, smoking continues to exert a significant effect on increasing the risk of developing and dying from CHD.

Smoking and Serum Lipids

The interaction of smoking and serum lipid levels in the development of CHD should be considered in the light of information concerning the relationship of smoking to serum lipid levels. Table A 7 presents studies which deal with the association between smoking and lipids, notably cholesterol, triglycerides, and lipoproteins (concerned with lipid transport). While some of the studies have indicated that smokers show increased serum levels of these lipid constituents, others have not. The populations investigated and the methods of the various studies show significant variation. This lack of comparability makes interpretation of the findings difficult.

It is clear, however, that in the presence of high serum cholesterol, cigarette smoking increases the risk of CHD. Figure 4 depicts the data from the Chicago Peoples Gas, Light and Coke Company study which show that smoking greatly increases the risk of CHD in each of the cholesterol groups.

Smoking and Hypertension

Some epidemiological studies have indicated that smokers tend to have lower mean systolic and/or diastolic blood pressures than nonsmokers, while other studies have not found this to be the case (table A 8). Reid, et al. (*155*), in a study of 1,300 British and American postal workers, found that the blood pressure difference between the smoking and nonsmoking groups was eliminated after controlling for body weight.

Tables 9 through 11, derived from the study by Borhani, et al. (*27*), demonstrate the following associations: That for both smokers and nonsmokers, the risk of dying from CHD increases with increasing diastolic or systolic pressure, and that the risk of mortality from CHD is higher among smokers than among nonsmokers in each blood pressure group. Cigarette smoking, therefore, has been shown to elevate CHD mortality independently both of its effect on blood pressure and of the effect of hypertension on CHD.

Smoking and Physical Inactivity

The recent study by Shapiro, et al. (*172*) of more than 110,000

TABLE 9.—*Death rates from coronary heart disease, by systolic blood pressure: ILWU mortality study 1951–61*

(Coronary heart disease as classified under ISC Code 420)

Age group	Systolic blood pressure in 1951	Smokers: Person-years of observation	Smokers: Death rate[1]	Nonsmokers: Person-years of observation	Nonsmokers: Death rate[1]
45–54	<130	1,877	27	2,413	8
	130–149	2,066	54	2,012	17
	150–169	740	95	1,177	26
	>170	369	109	672	45
55–64	<130	1,067	84	1,550	[2]6
	130–149	1,380	94	2,401	[2]25
	150–169	647	93	1,553	45
	>170	524	210	1,117	125

[1] Rate per 10,000 person-years of observation.

[2] $p<0.025$.

[3] $p<0.01$

SOURCE: Borhani, N. O., et al. (27).

TABLE 10.—*Death rates from coronary heart disease, by diastolic blood pressure: ILWU mortality study, 1951–61*

(Coronary heart disease as classified under ISC Code 420)

Age group	Diastolic blood pressure in 1951	Smokers: Person-years of observation	Smokers: Death rate[1]	Nonsmokers: Person-years of observation	Nonsmokers: Death rate[1]
45–54	<80	1,527	26	1,700	6
	80– 89	2,115	47	2,947	17
	90– 99	961	52	1,507	33
	>100	448	89	1,020	29
55–64	<80	1,059	104	1,447	[2]21
	80– 89	1,521	59	2,704	15
	90– 99	669	194	1,521	[2]46
	>100	369	163	954	147

[1] Rate per 10,000 person-years of observation.

[2] $p<0.05$.

[3] $p<0.01$.

SOURCE: Borhani, N. O., et al. (27).

TABLE 11.—*Death rates from coronary heart disease, among hypertensives and nonhypertensives: ILWU mortality study, 1951–61*

(Coronary heart disease as classified under ISC Code 420)

Age group	Blood pressure status[1]	Smokers: Person-years of observation	Smokers: Death rate[2]	Nonsmokers: Person-years of observation	Nonsmokers: Death rate[2]
45–64	Hypertensives	883	125	1,871	[3]32
	Nonhypertensives	4,169	29	5,303	13
55–64	Hypertensives	931	150	2,219	86
	Nonhypertensives	2,687	93	4,407	[3]16

[1] According to the WHO recommendation, the following cut-off points are recommended for the definition of hypertension:

(1) Normotension—below 140/80 mm. Hg.

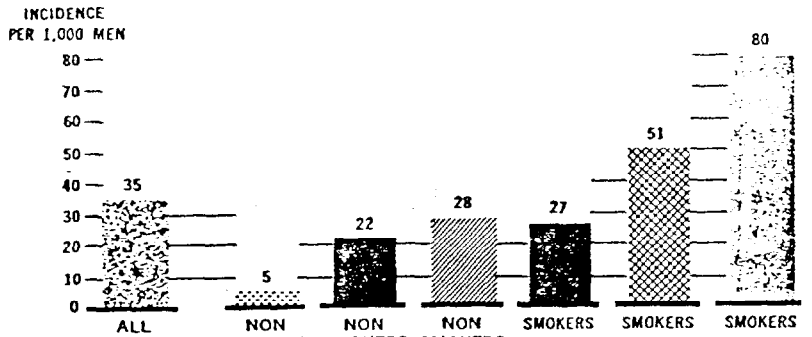
(2) Hypertension—systolic blood pressure 160 mm. Hg. or over, or diastolic 95 mm. Hg. or over, or both.

(3) Borderline—the residual category. In this analysis, Normotensives and Borderlines were combined and the population was grouped into 'Nonhypertensives' (1 and 3) and 'Hypertensives' (2).

[2] Rate per 10,000 person-years of observation.

[3] $p<0.01$.

SOURCE: Borhani, N. O., et al. (27).



CHD	46*	1	5	2	9	16	12
N	1329*	187	235	71	336	317	151
AGE	49	49	50	51	50	49	50
SYSTOLIC PRESSURE	134	133	136	139	131	133	135
WEIGHT RATIO	1.16	1.19	1.21	1.18	1.12	1.15	1.17

FIGURE 4—Relationship between smoking status and serum cholesterol level at initial examination, and incidence of clinical coronary heart disease in men originally age 40–59, free of definite CHD, and followed subsequently without systematic intervention, Peoples Gas Light and Coke Company study, 1958–1962. *For 34 men, no information on smoking status was available; one of these men had a coronary episode.

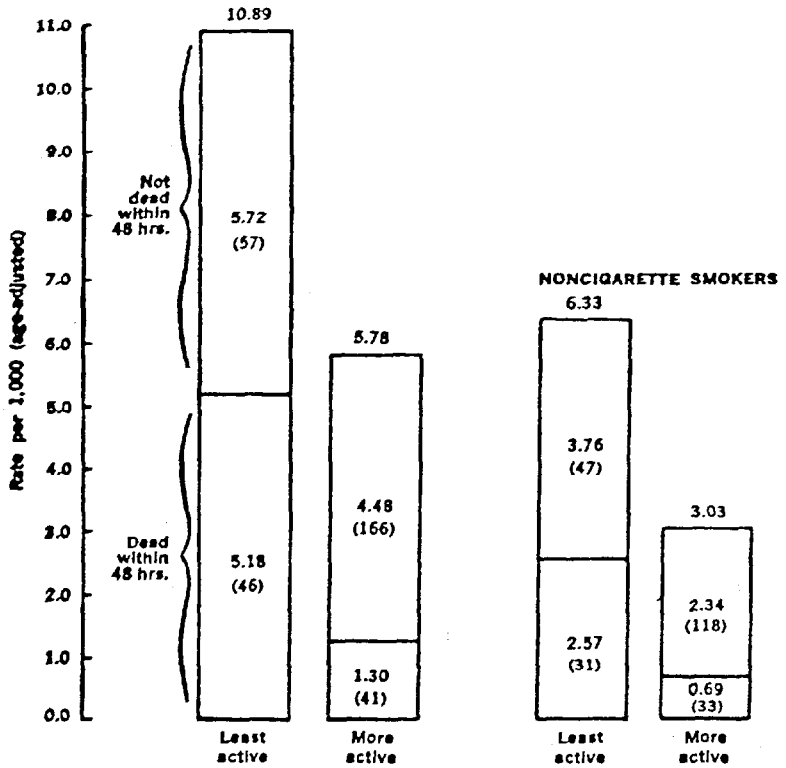
SOURCE: Stamler, J., et al. (*177*).

persons participating in the Health Insurance Plan of New York City has further identified and elaborated upon the interaction of the various risk factors. Physical inactivity, both in employment and during leisure time, was found to be a potent risk factor for the development of CHD, particularly for rapidly fatal myocardial infarction.

Figure 5 depicts the effect which smoking exerts on CHD in combination with physical inactivity. Of note, also, is the observation that within each activity grouping, smoking greatly increases the risk of myocardial infarction, thus exerting an independent effect.

Smoking and Obesity

The analysis by Truett, et al. (*190*) of the risk factor data from the Framingham study revealed that weight, while a significant risk factor, had a considerably smaller effect on CHD incidence than serum cholesterol, cigarette smoking, or elevated blood pressure. The results concerning the interaction of smoking and obesity from the San Francisco longshoremen study are shown in table 12.



Note: Both for cigarette smokers and noncigarette smokers differences between rates among the least and more active men are statistically significant for total MI and rapidly fatal MIs at the 0.99 confidence level. For other MIs the difference is statistically significant only for the nonsmokers (confidence level 0.95).

FIGURE 5—Average annual incidence of first myocardial infarction among men in relation to overall physical activity class and smoking habits (age-adjusted rates per 1,000)

(Actual number of deaths or myocardial infarctions are represented by figures in parentheses)

SOURCE: Shapiro, S., et al. (*172*).

This table shows that cigarette smokers in the 55 to 64 year age group were observed to have higher CHD death rates than nonsmokers in all weight categories. Similar findings, although not in all weight groups, were observed for the 45 to 54 year age group. Cigarette smoking is thus shown to be a CHD risk factor independent of body weight.

TABLE 12.—*Death rates from coronary heart disease among men without abnormalities related to cardiopulmonary diseases by weight classification in 1951: ILWU mortality study, 1951–61*

(Coronary heart disease as classified under ISC Code 420)

Age group	Weight classification [1]	Smokers		Nonsmokers	
		Person-years of observation	Death rate [2]	Person-years of observation	Death rate [2]
45–54	Not overweight	388	21	279	7
	Slightly overweight	962	28	1,096	0
	Moderately overweight	1,383	28	1,574	28
	Markedly overweight	1,055	22	1,797	0
55–64	Not overweight	222	43	247	0
	Slightly overweight	536	75	605	36
	Moderately overweight	855	109	1,320	[3]11
	Markedly overweight	735	88	1,653	[3]12

[1] The four classes are defined in the text.

[2] Rate per 10,000 person-years of observation.

[3] $p<0.01$.

SOURCE: Borhani, N. O., et al. (*27*).

TABLE 13.—*Death rates from coronary heart disease, by electrocardiographic findings in 1951: ILWU mortality study, 1951–61*

(Coronary heart disease as classified under ISC Code 420)

Age group	Electrocardiographic findings in 1951	Smokers		Nonsmokers	
		Person-years of observation	Death rate [1]	Person-years of observation	Death rate [1]
45–54	Abnormal	586	102	1,020	39
	Normal	4,454	38	6,134	15
55–64	Abnormal	583	223	1,149	96
	Normal	3,031	86	5,479	[2]31

[1] Rate per 10,000 person-years of observation.

[2] $p<0.005$.

SOURCE: Borhani, N. O., et al. (*27*).

TABLE 14.—*1958 status with respect to heart rate, blood pressure, cigarette smoking, and 10-year mortality rates, by cause (1,329 men originally age 40–59 and free of definite coronary heart disease) Peoples Gas Co. Study, 1958–68*

1958 risk factor status			Number of men	Ten-year mortality, 1958-68			
				All causes		CHD	
Heart rate	Cigarette smoking	Diastolic pressure		Number	Rate	Number	Rate
NH	NH	NH	378	20	[1]48.3	5	[1]12.0
H	NH	NH	45	6	114.9	3	70.3
NH	NH	H	107	14	118.3	6	51.8
H	NH	H	30	8	221.6	3	82.0
NH	H	NH	491	57	116.8	19	38.9
H	H	NH	127	22	171.1	8	62.3
NH	H	H	103	22	190.4	6	55.0
H	H	H	44	13	265.4	5	94.9
All			1,325	162	113.2	55	39.4

[1] Rate per thousand. All rates are age-adjusted by 5-year age groups to U.S. male population, 1960. High (H): Heart rate $\geq$80; $\geq$10 cigarettes per day; diastolic blood pressure $\geq$90 mm. Hg. NH is not high, i.e., below specified cutting points.

[2] No smoking data available on 4 of the 1,329 men.

SOURCE: Berkson, D. M., et al. (*25*).

TABLE 15.—*The effect of the cessation of cigarette smoking on the incidence of CHD*

(Incidence ratios—actual number of cases or events are shown in parentheses)

Author, year, country, reference	Results		Comments
	All CHD events	*All myocardial infarction*	
Jenkins et al., 1968 U.S.A. (90).	Never smoked .....1.00(30)	1.00(21)	
	Current cigarette smokers .....2.36(84)	2.78(68)	
	Former cigarette smokers .....2.15(19)	2.47(15)	
	Death from CHD		
	Smoked 1–19 cigarettes/day	*Smoked >20 cigarettes/day*	
Hammond and Garfinkel, 1969. U.S.A. (78).	Never smoked regularly .....1.00(1,841)	1.00(1,841)	Male data only
	Current cigarette smokers .....1.90(1,063)	2.55(2,822)	
	Stopped <1 year 1.62 (29)	1.61 (62)	
	1–4 .....1.22 (57)	1.51 (154)	
	5–9 .....1.26 (55)	1.16 (135)	
	10–19 .....0.96 (52)	1.25 (133)	
	>20 .....1.08 (70)	1.05 (80)	
	All ex-cigarette smokers ..1.16 (263)	1.28 (564)	
	Total definite myocardial infarction		
Shapiro et al., 1969, U.S.A. (171).	Never smoked 1.00		
	Current cigarette smokers 1.87		
	Stopped ≦5 years 0.76		
	All CHD deaths	*First major coronary event*	
Pooling Project, American Heart Association 1970, U.S.A. (88).	Never smoked .....1.00(27)	1.00 (53)	See table 4 for description of Pooling Project.
	>½ pack/day .....1.65(34)	1.65 (72)	
	1 pack/day .....1.70(86)	2.08(205)	
	>1 pack/day .....3.00(68)	3.28(154)	
	Ex-smokers .....0.80(19)	1.25 (51)	

TABLE 16.—*Annual probability of death from coronary heart disease, in current and discontinued smokers, by age, maximum amount smoked, and age started smoking*

Age	Maximum daily number of cigarettes smoked	Age started smoking 15–19		Age started smoking 20–24	
		Current smokers	Discontinued for five or more years	Current smokers	Discontinued for five or more years
		(Probability $\times 10^{-6}$)			
55–64	0	501	—	501	—
	10–20	798	568	811	551
	21–39	969	766	872	698
65–74 [1]	0	1,015	—	1,015	—
	10–20	1,501	1,169	1,478	1,218
	21–39	1,710	1,334	1,573	1,098

[1] For age group 65–74, probabilities for discontinued smokers are for 10 or more years of discontinuance since data for the 5–9 year discontinuance group are not given.

SOURCE: Cornfield, J., Mitchell, S. (55).

Based on data derived from Kahn, H. A. (88).

Smoking and Electrocardiographic Abnormalities

Electrocardiographic (ECG) abnormalities such as T-wave and ST-segment changes as well as a number of arrhythmias are useful indicators of CHD and may, therefore, be predictive of the development of clinically overt CHD manifestations. The results summarized in table 13, from the prospective study by Borhani, et al. (*27*), reflect the joint predictive value of smoking and ECG abnormalities on the death rate from CHD.

Smoking and Heart Rate

Recent analysis by Berkson, et al. (*23*) of the data derived from the Chicago Peoples Gas, Light and Coke Company study of middle-aged men revealed that resting heart rates of 80 or greater were associated with an increase in the risk of death from CHD. These authors found that this association was independent of the other major coronary risk factors.

Table 14 presents the interaction between smoking, blood pressure, and elevated heart rate in increasing the risk of CHD mortality. This study shows that cigarette smoking increases CHD risk in the presence of elevated heart rate as well as in its absence.

THE EFFECT OF CESSATION OF CIGARETTE SMOKING ON CORONARY HEART DISEASE

A number of epidemiological studies have been concerned with the CHD incidence and mortality among ex-cigarette smokers as compared with current smokers (*51, 76, 88, 90, 93, 172*). These studies are listed in table 15. Table 16 presents the data derived by Cornfield and Mitchell (*45*) from the Dorn Study of U.S. Veterans (*93*).

Ex-cigarette smokers show a reduced risk of both myocardial infarction and death from CHD relative to that of continuing cigarette smokers. The Pooling Project (*88*) and the Western Collaborative Study Group (*192*) which adjusted for the other risk factors of elevated serum cholesterol and blood pressure observed this relationship. Hammond and Garfinkel (*76*) noted that cessation of smoking is accompanied by a relative decrease in risk of death from CHD within 1 year after stopping.

This decreased risk of CHD among ex-smokers further strengthens the relationship between smoking and CHD. It must be noted, however, that the group of ex-smokers is composed of individuals who have stopped smoking for a variety of reasons. Those who stop because of ill health and the presence of symptoms are generally at high risk and can bias the group results in one direction;

those healthy persons who stop as part of a general concern about their health and may adopt a number of self-protective health practices are generally at low risk and can bias the group results in the other direction. Therefore, ex-smokers as a group are not fully representative of the entire population of smokers and may have limited value in predicting what would happen if large numbers of cigarette smokers stopped smoking purely for self-protection. Certain incidence studies, such as the Pooling Project (*88*), were initiated with only clinically healthy individuals. The data from such studies, as well as those from the British physicians study, contain ex-smoker data less influenced by these biases.

Fletcher and Horn (*63*) have recently presented data derived from the British physicians study of Doll and Hill. Over the past 10-15 years, cigarette smoking rates among British physicians have declined significantly in comparison with those of the general British population. The information presented by these authors concerning all cardiovascular diseases showed that for individuals between the ages of 35 and 64, the age-adjusted death rate for CHD declined by 6 percent among physicians and rose by 10 percent among the male population of England and Wales during the period from 1953–57 to 1961–65.

THE CONSTITUTIONAL HYPOTHESIS

The effect of smoking on the incidence of CHD has been found to be independent of the influence of the other CHD risk factors. When such risk factors as high serum cholesterol (*177*), increased blood pressure (*27*), elevated resting heart rate (*23*), physical inactivity (*172*), obesity (*27*), and electrocardiographic abnormalities (*27*) have been controlled, cigarette smokers still show higher rates of CHD than nonsmokers.

It has been suggested by some (*39, 170*) that the relationship between cigarette smoking and CHD has a constitutional basis. That is people with certain constitutional make-ups are more likely to develop CHD, and the same people are more likely to smoke cigarettes. This hypothesis maintains that the relationship between cigarette smoking and CHD is thus largely fortuitous and that the significant relationships are between the genetic make-up of the individual and CHD and between the genetic make-up of the individual and his becoming a cigarette smoker. Two sets of epidemiologic data bear on this hypothesis.

It has been maintained that people with a certain temperament are more likely to smoke and also more likely to develop CHD. These characteristics have been demonstrated for those with the

Type A behavior pattern of Rosenmann, et al. (*159*) which is characterized by competitiveness, excessive drive, and an enhanced sense of time urgency. The prospective study organized by the Western Collaborative Group indicates that individuals who exhibit this type of personality are more likely to have or develop CHD than those without it (Type B), whether or not they smoke. When the incidence rates of CHD are analyzed with respect to smoking and personality types (tables A 17, A 18), it is noted that in both Type A and Type B individuals the incidence of CHD is greater among cigarette smokers than among nonsmokers. This research indicates that both personality type, as measured in these studies, and cigarette smoking contribute independently as risk factors to the development of CHD. To what extent such behavior patterns are determined constitutionally or represent acquired characteristics is still open to question.

The other type of research designed to study the genetic hypothesis has made use of data from registries of twins. Cederlof, et al. (*37, 38, 39, 40*) have utilized the Twin Registries of Sweden and the Veterans Follow-Up Agency of the U.S. National Academy of Sciences–National Research Council to investigate the relative contributions of heredity and smoking to cardiovascular and bronchopulmonary symptom prevalence. Data obtained by mailed questionnaires were analyzed for the following characteristics: zygosity of the same-sex twin pair, urban-rural residence differences, smoking concordance, and history of various symptoms. Comparisons were made between smoking discordant monozygotic (identical) pairs and smoking discordant dizygotic (fraternal) pairs, and between unmatched twin pairs and matched twin pairs. Smoking discordance has been defined somewhat differently in various reports but, in general, describes twin pairs in which the smoking habits differ between the two members of the same twin pai

Analyzing the data obtained from 9,319 Swedish twin pairs (72.3 percent of the possible respondents), Cederlof, et al. (*39*) found that respiratory symptoms were more common among smokers in both the unmatched and matched smoking discordant twin pair groups. The authors analyzed the data in two distinct manners. Group A analysis, which did not control for genetic factors utilized two groups; the first composed of all the firstborn, and the second of those listed second on the birth certificates. Group B analysis utilized MZ and DZ twin pairs which were discordant for smoking, thereby controlling genetic factors. "Angina pectoris," as defined by a certain pattern of responses to the questionnaire, was found to be more prevalent among smokers in Group A, but this difference was not present when the data from Group B were analyzed. Males in the first group exhibited a "hypermorbidity ratio"

of 1.6, while those in the second group were found to have one of approximately 1.1. The authors concluded that this difference between the two groups provides better support for the importance of constitutional factors as against the importance of cigarette smoking in the development of angina pectoris.

A similar study was done using the responses of 4,379 U.S. Veteran twin pairs (approximately 60 percent of estimated available total) who completed the mailed questionnaires (*38*). Cederlof, et al. found a significantly increased prevalence of chest pain and "angina pectoris" among smokers when Group A was analyzed. Analysis of the smoking-discordant matched twin pairs (Group B) revealed no association between smoking and cardiovascular symptoms among the monozygotic pairs. The dizygotic pair data did show a slight association. The authors concluded that this lack of association among the monozygotes and its presence among the dizygotes and unmatched pairs strengthens the case for a constitutional hypothesis.

A major problem in these studies is the small number of cases available and, therefore, the statistical instability of the results. In the Swedish study, among the 274 monozygotes, only 19 smokers and 16 nonsmokers were classified as having angina pectoris while among the 733 dizygotes, 25 smokers and 25 nonsmokers were so classified. In neither group was the difference between the prevalence ratios found in the Group A analysis and that in the Group B analysis of statistical significance. Analysis of the data on women shows a similar lack of significance.

Similar criticisms may be made of the study which utilized the U.S. Veteran Twin Registry. In that study, the authors observed that the difference in the prevalence of angina pectoris between the low-cigarette-exposure and high-cigarette-exposure dizygotic groups was not present among the monozygotes. The authors questioned whether the excess morbidity associated with cigarette smoking found in the dizygotic group was causal as it was not possible to reproduce the association when studying monozygotic smoking-discordant twin pairs. As noted above, the numbers in this study are also small so that the differences in rates do not approach statistical significance.

Tibblin (*188*) has questioned the value of a mailed questionnaire to diagnose heart disease. The questionnaire as originally constructed was used and validated by interview technique alone (*157, 158*). Cederlof, et al. (*40*) conducted a study to determine the validity of this questionnaire as a mailed instrument by personally interviewing and examining 170 of the twin pairs who had replied. Of the eight males who were diagnosed as having "angina pectoris" by the questionnaire, four were found to be free of symptoms on

clinical examination, while among 204 responding negatively, two were found to have angina by clinical criteria. None of the 11 women who were diagnosed as positive by questionnaire was found to be clinically affected, and of the 136 reporting as negative, three had symptoms of angina pectoris.

Other major difficulties associated with these studies include the problems of using prevalence data in the investigation of a disease (CHD) from which a significant number of those affected die shortly after the onset of symptoms, the inclusion of ex-smokers in the smoking population, and the low numbers of heavy cigarette smokers in the Swedish population.

In general, the problems of using twin registries to study the etiology of cardiovascular disease with mortality and morbidity ratios in the neighborhood of 2 to 1 are much more difficult than in studying the etiology of bronchopulmonary disease in which the relationships are of the order of magnitude of 4 to 1.

More recently, Friberg, et al. (*69*) reported on mortality data from the Swedish Twin Registry. The authors suggested that part of the increased mortality observed among smokers when compared with nonsmokers was not due to smoking per se but to factors associated with smoking. The very small numbers of total deaths presently available (47 deaths among 706 dizygotic pairs and 13 deaths among 246 monozygotic pairs) do not provide a statistically stable base for deriving any conclusions at the present time.

Hauge, et al. (*81*) have recently reported on the influence of smoking on the morbidity and mortality observed in the Danish Twin Register. Among 762 monozygotic and same-sexed dizygotic twin pairs, angina pectoris was found to be significantly more frequent in those cotwins with a higher consumption of tobacco than in those with a lower or no consumption. A similar tendency was observed for myocardial infarctions but was not of statistical significance.

Seltzer, who has been a proponent of the constitutional hypothesis, in a recent review of some of the experimental, clinical, and pathological data relating smoking and CHD, concluded that the evidence from these areas has not "reasonably substantiated" the "hypothesis" of the acute effect of cigarette smoking on the coronary circulation, nor has the chronic effect of cigarette smoking on the cardiovascular system been shown to be a "clear" and consistent one (*170*). His views are contrary to those of most researchers in this field.

Although the data from the twin studies are inconclusive with regard to a role for genetic factors in heart disease, it would be surprising if genetic factors did not play such a role. It is open to

question whether findings from twin studies can be used to distinguish between the hypothesis that genetic factors govern the level of host susceptibility or resistance to the effects of an exogenous influence such as cigarette smoking and the hypothesis that genetic factors "cause" both heart disease and smoking.

AUTOPSY STUDIES RELATING SMOKING, ATHEROSCLEROSIS, AND SUDDEN CHD DEATH

A number of researchers have investigated the cigarette smoking habits and the cardiovascular pathology of those individuals dying suddenly from CHD and of large populations of individuals with and without histories of overt CHD.

Spain and Bradess (*175*) recently analyzed the smoking habits of 189 individuals who died suddenly and unexpectedly, apparently from the first acute clinical episodes of CHD. The authors noted a close correlation of a history of cigarette smoking with this type of sudden death and also with shorter survival times following the acute episode. This association was strongest in those persons under 50 years of age.

The authors also observed that those surviving very short periods of time showed a notable lack of intracoronary artery thrombi at autopsy and that the frequency of thrombi present increased with increasing survival time. They suggested that thrombi found at autopsy may be the result rather than the cause of certain instances of myocardial infarction, particularly of lesions showing subendocardial necrosis. This finding is of significance in the study of the effect of smoking on myocardial metabolism and oxygen supply and demand rather than on thrombus or platelet plug formation.

While the autopsy study of Spain and Bradess (*175*) concerned sudden death among smokers, other autopsy studies from various countries have been directed towards the relationship of cigarette smoking to the presence of atherosclerotic disease in the aorta and coronary arteries. These are concerned with the long-term effects which smoking has on the cardiovascular system and are summarized in table 19. The studies of Auerbach, et al. (*12*), Avtandilov, et al. (*13*), Sackett, et al. (*165*), and Strong, et al. (*182*) found that aortic and coronary atherosclerosis were more common and more severe among smokers than among nonsmokers. Auerbach, et al. (*12*) noted that this relationship persisted when the cases were matched for both age and cause of death or when the following cases were excluded; men with a history of diabetes; men who had died of any type of heart disease; and men whose hearts weighed 400 grams or more. Sackett, et al. (*165*) found that the

TABLE 19.—*Autopsy studies of atherosclerosis*

(Figures in parentheses are number of individuals in that smoking category)[1]

[SM = smokers NS = nonsmokers]

Author, year, country, reference	Autopsy population	Data collection	Cigarettes per day	Conclusions	Comments
Wilens and Plair, 1962, U.S.A. (*114*).	989 consecutive male autopsies at New York City VA hospitals.	Routine clinical records of previous and present admissions.	*Severity of aortic sclerosis* *Above average* / *Average* / *Below average* NS ..... 9.9 (161) / 60.2 / 29.8 <20 ..... 19.1 (152) / 63.2 / 17.8 20–30 ..... 26.4 (288) / 62.5 / 11.1 >30 .....†25.1 (199) / 61.3 / †13.6	The authors conclude that in 60 percent of cases, the degree of sclerosis at autopsy was commensurate with age of patient, regardless of smoking habits. In the remaining 40 percent there is evidence that cigarette smoking may be associated with an above-average degree of aortic sclerosis.	Smoking data unavailable for 120 cases. Each aorta specimen given an "atherosclerotic age" by comparison with a standard. If "atherosclerotic age" was found to be 10 years more than real age, the aorta was said to show above-average sclerosis. †$p<0.001$ comparing 9.9 with 25.1 and 29.8 with 13.6.
Auerbach, et al., 1965, U.S.A. (*11*).	1,372 autopsies of male patients in Orange, New Jersey, VA hospital for whom smoking habit data were available and who did not have overt CHD at death.	Interview with next of kin.	*Degree of coronary artery atherosclerosis (overall age-adjusted results)* *No atherosclerosis* / *Slight* / *Moderate* / *Advanced* NS .....5.6 (69) / 57.3 / 21.8 / 15.3 Current cigarette <20 .....2.6 (139) / 30.9 / 37.3 / 29.2 20–39 .....0.8 (299) / 19.7 / 42.1 / 37.4 >40 .....0.6 (144) / 18.1 / 35.4 / 45.9	The authors conclude that the percentage of men with an advanced degree of coronary atherosclerosis was higher among cigarette smokers than among nonsmokers and that the percentage increased with amount of cigarette smoking. This relationship persisted even when cases were matched for age and cause of death.	

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

TABLE 19.—*Autopsy studies of atherosclerosis (cont.)*

(Figures in parentheses are number of individuals in that smoking category)[1]

[SM = smokers NS = nonsmokers]

Author, year, country, reference	Autopsy population	Data collection	Cigarettes per day	Conclusions	Comments
Avtandilov, 1965, Russia (*13*).	259 male and 141 female autopsies.	Not specified, but there were: 180 SM and 220 NS.	*Comparative size of mean area of atherosclerotic lesions in inner coat of coronary arteries.* *Right coronary artery* / *Left coronary artery* *SM* / *NS* / *SM* / *NS* 30–39 .. †15.5 (80) / 1.3 (82) / †6.3 / 2.2 40–49 .. †23.6 (84) / 11.5 (27) / †15.8 / 4.4 50–59 .. †36.3 (89) / 14.8 (39) / †27.9 / 9.9 60–69 .. †31.9 (32) / 23.8 (86) / †26.5 / 22.5 70–79 .. 41.9 (18) / 31.7 (86) / 26.1 / 35.8	The author concludes that the worst changes were found in the left and right coronary arteries with less severe changes in circumflex artery and aorta.	Causes of death 96-atherosclerotic, 102-accidental, 202-various diseases. †T-test for significance of difference between means is significant at $p<0.05$ level.
Sackett, et al., 1968, U.S.A. (*165*).	893 total, including 433 male and 460 female (white) patients autopsied at Roswell Park Memorial Hospital. Represents all deaths 1956–1964 exclusive of 81 male pipe and cigar smokers and 55 incomplete files.	Patient interview on admission.	The results concerning aortic atherosclerosis are given in form of figure presentation of ridit-analysis.	The authors conclude that among males, "... a large increase in the severity of aortic atherosclerosis occurred in the groups using either cigarettes only or both cigarettes and alcohol as compared with the group using neither cigarettes nor alcohol ... there was only a small and statistically insignificant difference between the group using cigarettes alone and the group using both cigarettes and alcohol, ..." The severity of aortic atherosclerosis increased with increasing use of cigarettes, when measured both by intensity and by duration of smoking.	

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

TABLE 19.—*Autopsy studies of atherosclerosis (cont.)*

(Figures in parentheses are number of individuals in that smoking category)[1]

[SM = smokers NS = nonsmokers]

Author, year, country, reference	Autopsy population	Data collection	Cigarettes per day	Conclusions	Comments
Viel et al., 1968 Chile (*200*)	1,150 males and 290 females who died violently in 1961–1964. Smoking information available only on 566 males.	Interview with relatives.	The results concerning internal fibrous streaks and fatty plaques in the left anterior descending coronary artery are reported in graphic form only. An examination of this data indicates that the moderate and heavy smokers appeared to show consistently higher percentages of diseased areas than the nonsmokers. But the statement of the authors implies that these differences were not statistically significant when subjected to an analysis of variance.	The authors conclude that: "No relationship between atherosclerotic lesions and the use of tobacco was discernible."	
Strong et al., 1969 U.S.A. (*188*)	747 males 20–64 years of age autopsied between 1963–1966 at Charity Hospital in New Orleans.	Interview with next of kin within 8 weeks of death.	*Basal Group (excluding diseases related to smoking or CHD). Mean percentage of coronary artery internal surface involved with raised lesions (number of cases).* *White* *25–34* *35–44* *45–54* *55–64* NS ..... 2 (5) 19(14) 20 (6) 30(11) 1–24 cigarettes/day .... 9(14) 17(10) 26(16) 39 (7) >25 cigarettes/day ....12 (9) 31(14) 26(25) 39(20) *Negro* NS ..... 4(14) 3 (8) 16(11) 17(14) 1–24 cigarettes/day .... 3(39) 11(31) 14(30) 28(22) >25 cigarettes/day ....17(10) 14(17) 29(12) 16(11)	The authors conclude that: "Atherosclerotic involvement of aorta and coronary arteries is greatest in heavy smokers and least in nonsmokers."	This report concerns only ages 25–64. No data on statistical significance provided.

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

severity of aortic atherosclerosis, as measured both by intensity and duration, increased with increasing use of cigarettes and that this dose-relationship persisted when the patients were matched for the consumption of alcohol. On the other hand, Viel, et al. (*200*) concluded from their study of accidental deaths in Chile that "no relationship between atherosclerotic lesions and the use of tobacco was discernible." Examination of the data (provided in graph form only) indicates that heavy smokers showed consistently higher percentages of diseased areas than nonsmokers, but apparently these differences were not statistically significant when subjected to an analysis of variance.

Thus, in addition to the acute effects which smoking exerts on cardiovascular physiology, cigarette smoking is associated with a significant increase in atherosclerosis.

EXPERIMENTAL STUDIES CONCERNING THE RELATIONSHIP OF CORONARY HEART DISEASE AND SMOKING

Several areas of interest in cardiovascular pathophysiology have been investigated in the search for the mechanisms by which cigarette smoking contributes to cardiovascular disease, particularly coronary artery disease. Previous Public Health Service Reviews (*191, 192, 193, 198*) have described in detail and commented on the results of experiments by many teams of researchers.

Central to the discussion which follows is a concept of cardiac physiology which provides a framework for analysis and understanding of the varied research. That concept concerns the dynamic balance between myocardial oxygen need and supply.

Cardiovascular Effects of Cigarette Smoke and Nicotine

The inhalation of tobacco smoke or the parenteral administration of nicotine has been found by many researchers to be associated with a number of specific acute cardiovascular responses. These responses have been observed in human as well as animal subjects, including increased heart rate, blood pressure, cardiac output, stroke volume, velocity of contraction, myocardial contractile force, myocardial oxygen consumption, arrhythmia formation, and electrocardiographic or ballistocardiographic changes (tables A 20 to A 22). The effect of these responses on coronary blood flow will be discussed in a following section.

That the acute effects observed following the inhalation of cigarette smoke are due primarily to the nicotine present in the smoke may be seen in the results of a number of experiments. In humans, Irving and Yamamota (*89*) and Von Ahn (*202*) duplicated the

effects of cigarette smoking by the administration of nicotine intravenously. Similar results in animals were noted by Kien and Sherrod (*112*).

The mechanism by which cigarette smoke and hence nicotine induces these changes has been of interest to numerous investigators. Nicotine has long been known as a stimulator of both sympathetic and parasympathetic ganglia. Research has centered, therefore, on the function of catecholamines, mainly epinephrine and norepinephrine, as mediators, of these responses. Using isolated rabbit atrial myocardium, Burn and Rand (*35*) noted that the prior administration of reserpine to the perfusate blocked the increased rate and amplitude of contraction seen following the administration of nicotine. West, et al. (*208*) showed that the *in vivo* cardiac stimulating effect of nicotine was blocked by tetraethylammonium chloride. Leaders and Long (*125*), Romero and Talesnik (*156*), and, more recently, Ross and Blesa (*160*) have all demonstrated this blockade in animals using agents such as pentolinium, hexamethonium, guanethidine, and reserpine.

More direct evidence of the catecholamine-releasing effect of nicotine has been found by Watts (*203*) and Westfall, et al. (*209, 210, 211*) (table A22). Among animal subjects, nicotine administration and the inhalation of the smoke of standard cigarettes caused significant increases in peripheral arterial epinephrine levels, while cornsilk cigarette smoke inhalation evoked no such change. In humans, cigarette smoking was found to be associated with a significant increase in urinary epinephrine excretion.

The source of these nicotine-released catecholamines, particularly those which mediate the immediate and local cardiac responses to intracoronary injections of nicotine, is felt to be the myocardial chromaffin tissue (*35, 160*). The more widespread effects are most probably mediated by hormones released from the adrenal gland.

According to recent research of Saphir and Rapaport, catecholamine release may not be the sole mediator of these responses (*166*). These investigators reported that intra-arterial injections of nicotine into the mesenteric circulation of cats were followed within 1 to 2 seconds by enhanced myocardial performance, increased left ventricular systolic pressure, and increased systemic resistance. Sectioning of the mesenteric afferent nerves led to a diminished response. The authors concluded that the cardiovascular response to nicotine may also be neurogenic in nature. Nadeau and James (*142*) injected nicotine directly into the sinus node artery of dogs and noted an initial bradycardia, due probably to direct vagal stimulation, followed by tachycardia, due probably to catecholamine release.

That the presence of nicotine may predispose the myocardium, particularly a hypoxic or previously damaged myocardium, to arrhythmia formation is suggested by the research of Balazs, et al. (*16*), Bellet, et al. (*21*), and Greenspan, et al. (*74*). Balazs produced myocardial lesions in dogs either by pretreatment with isoproterenol or ligation of the anterior descending coronary artery. It was found that while normal animals did not develop arrhythmias upon challenge with small doses of intravenous nicotine, the animals with damaged myocardiums responded with increased arrhythmia formation shortly after their spontaneous arrhythmias had ceased. More recently, Bellet, et al. (*20*) studied the effect of cigarette smoke inhalation on the ventricular fibrillation threshold in anesthetized dogs. They observed a statistically significant decrease in the threshold following smoke inhalation. Greenspan, et al. (*74*), using isolated dog right ventricular myocardium, observed that nicotine perfusion increased the automaticity of the Purkinje fibers system and decreased the conduction velocity. The authors consider that these two nicotine-induced effects probably predispose the myocardium to the initiation of arrhythmias.

Coronary Blood Flow

Studies in animals and humans (tables A20, A21) have noted alterations in coronary blood flow (CBF) following the inhalation of cigarette smoke or the administration of nicotine. Generally, exposure of the normal subject to these agents results in an increase in flow. Kien and Sherrod (*112*), Leb, et al. (*126*), Ross and Blesa (*160*), Travell, et al. (*189*), and West et al. (*208*), working with normal animals, and Bargeron, et al. (*17*), working with normal humans, have demonstrated this response. As with the other cardiac responses to the administration of nicotine, it has been found that the augmentation in CBF is most probably due to the release of catecholamines. Using instantaneous coronary arterial flow measurement in dogs, Ross and Blesa (*160*) were able to reproduce the effects of intracoronary nicotine with the administration of epinephrine and were able to block the response to nicotine by pretreatment with pentolinium.

The direct action of catecholamines on the coronary arteries may not, however, be solely responsible for the increase in CBF seen with cigarette smoking and intravenous nicotine administration. It appears that the catecholamine-induced increase in myocardial work and therefore in myocardial oxygen requirement is a prerequisite for the increase in CBF. Kien and Sherrod (*112*), using tracheostomized dogs, found that without blood pressure and cardiac output changes CBF did not increase following either the inhalation of cigarette smoke or the administration of nicotine

intravenously, although CBF did increase following such changes. Recent work by Leb, et al. (*126*) has utilized Rb^{84} as a radioactive marker in order to distinguish capillary flow from overall total CBF. The authors consider that this capillary flow represents that portion of CBF which is effectively involved in nutrient and oxygen exchange. The researchers observed that the increase in effective coronary flow was almost proportional to the nicotine-induced increase in myocardial oxygen consumption. However, the increase in total coronary flow which may be due to increased myocardial shunting was far in excess. Thus, the increased work evoked by the effect of nicotine on the myocardium may induce local hormonal release in the myocardium and coronary vessels leading to coronary vasodilatation and increased CBF.

This homeostatic response to increased work appears to be fully effective only in the subjects with normal coronary arteries. Bellet, et al. (*22*), working with normal dogs and dogs that had undergone either coronary artery ligation or artificially-induced coronary artery narrowing, noted that the increase in CBF following the intravenous administration of nicotine was significantly less among the animals with coronary insufficiency. Work with humans discussed above has revealed a similar increase in CBF with smoking in normals. Regan, et al. (*154*) studied seven men with EKG-proven myocardial infarction and observed that cigarette smoke evoked slight increases in myocardial oxygen consumption in only three patients and caused no overall rise in CBF. A number of other investigators have noted that patients with overt CHD do not respond to the stimulus of cigarette smoke as readily as do normals (*67, 149, 164*).

Thus, patients with compromised coronary circulation may not be capable of increasing their coronary flow in the face of the increased demands of a myocardium stimulated by nicotine or cigarette smoke. In the normal state, the heart responds to increased oxygen demands by increasing coronary flow because even at rest oxygen extraction is almost at a maximal level. Any further increase in extraction may produce coronary sinus pO_2 values incompatible with proper tissue oxygenation.

Cardiovascular Effects of Carbon Monoxide

Carbon monoxide (CO) is a colorless and odorless gas, low levels of which have significant effects on human and animal physiology which are just now beginning to be understood. According to Wynder and Hoffmann (*215*), it is present in cigarette smoke in concentrations of approximately 2.9 to 5.1 percent. The concentration of CO in smoke is subject to many factors, among them

the type of tobacco and the porosity of cigarette paper. The concentration of CO in smoke has been found to increase significantly toward the last puffs of the cigarette.

According to Chevalier, et al. (*41*), a concentration of approximately 4 percent CO in cigarette smoke will produce alveolar levels of around 0.04 percent which, equilibrated with hemoglobin, result in carboxyhemoglobin (COHb) concentrations of from 3 to 10 percent. A number of investigators have compared COHb levels in smokers and nonsmokers. Goldsmith and Landaw (*73*) reported the analysis of expired air samples obtained from 3,311 longshoremen. Using a regression analysis, they calculated the concentration of COHb and found that nonsmokers showed levels of 1.2 percent while those smoking over 2 packs per day had levels of 6.8 percent and that smokers of lesser amounts had intermediate levels. Occupational exposure accounted for the mean nonsmokers' level being over 1.0 percent, an unusual finding in comparison with other studies. Kjeldsen (*113*) interviewed and obtained blood samples from 934 CHD-free smokers and nonsmokers. The mean COHb level for 196 nonsmokers was 0.4 percent while all inhaling smokers had a mean level of 7.3 percent. All 416 cigarette smokers, regardless of inhalation or amount smoked, showed a mean level of 4.0 percent.

Carbon monoxide has many varied and significant effects on human physiology. An overall review of these effects may be found in a discussion by Lilienthal (*127*) or more recently in an extensive review by the United States Public Health Service National Air Pollution Control Administration (*194*). Apart from its effects on respiratory and circulatory function, CO has been found to affect certain central nervous system functions adversely. These effects are probably due to interference by CO with the proper oxygenation and oxidative metabolism of the tissue in question.

CO interferes with oxygen transport in a variety of ways. First, the affinity of hemoglobin for CO is approximately 200 times greater than its affinity for oxygen, and thus CO can easily displace oxygen from hemoglobin. Second, CO shifts the oxyhemoglobin dissociation curve. By increasing the avidity with which oxygen is bound by hemoglobin, CO interferes with O_2 release at the tissue level. This is of greatest importance at the tissue level where the oxygen content of the capillary blood has been reduced to approximately 40 percent saturation. Here the shift can substantially decrease the oxygen tension supplying the tissues.

Third, and of more recent note, is the possible interference by CO with the homeostatic mechanism by which 2, 3–diphosphoglycerate (2, 3–DPG) controls the affinity of hemoglobin for oxygen. Bunn and Jandl (*54*) have recently reviewed the various experi-

ments concerning this glycolytic intermediate. The question of whether the low levels of CO present in the blood of smokers can affect this homeostasis is presently under investigation (*29, 143*), and firm conclusions cannot be drawn at this time.

Apart from its effect on hemoglobin affinity, CO appears to induce arterial hypoxemia, and this may act as an additional cause of tissue hypoxia. Ayres, et al. (*14, 15*) observed unexpectedly that exposure of individuals to CO sufficient to raise their levels of COHb to between 5 and 10 percent was associated with a significant fall in arterial pO Greater fall in venous pO_2 was noted, but this was considered secondary to increased tissue extraction. In a recent article, Brody and Coburn (*30*) suggested that this COHb-induced arterial hypoxemia was due to the interaction of a number of factors. These authors noted that in the presence of veno-arterial shunts or of an imbalance in the ventilation-perfusion ratio, the shift in the oxyhemoglobin dissociation curve increased the alveolar-arterial O_2 gradient and resulted in arterial hypoxemia. The presence of shunts as small as 2 percent of cardiac output as well as of approximately 10 percent COHb was found to cause an increase in the gradient. Such ventilation-perfusion (V/Q) abnormalities have recently been noted even in asymptomatic smokers (see Chapter on Chronic Obstructive Bronchopulmonary Disease). The increased levels of COHb found in the blood of smokers may interact with these V/Q abnormalities to further decrease available oxygen.

In normal individuals, coronary flow can increase to meet the increased oxygen demands of a stressed myocardium (as that under nicotine stimulation), while in individuals with severe CHD coronary flow cannot respond as readily. In such cases, myocardial oxygen extraction must be increased above the almost maximal extraction found at rest. Any interference with arterial oxygen levels or hemoglobin affinity could very well decrease available oxygen supplies below the level required for proper tissue function. That this occurs is suggested by the experiments discussed below.

Chevalier, et al. (*41*) exposed 10 young nonsmokers to CO concentrations sufficient to induce COHb levels of approximately 4 percent. Taking measurements from blood specimens obtained at cardiac catheterization under resting and exercise conditions, the authors noted that the ratio of oxygen debt to oxygen uptake increased significantly under conditions of increased COHb. According to the investigators this implied that the same work was being done at a greater metabolic cost. These same authors (*121, 122*) had previously noted similar findings among smokers and observed

that cessation of smoking was associated with a significant improvement in oxygen debt accumulation.

More recent work by Ayres, et al. (*15*) has focused on the difference in response to CO exposure between 7 normals and 4 patients suffering from CHD (proven arteriographically). The induction of a COHb concentration of approximately 9 percent in the normals was followed by an increase in coronary blood flow, a decrease in hemoglobin-oxygen percent extraction and no change in myocardial oxygen consumption, coronary sinus oxygen tension, and lactate and pyruvate extraction ratios. The induction of similar COHb levels in the CHD patients was followed by no change in coronary blood flow, a decrease in the hemoglobin-oxygen extraction ratio, and no change in myocardial oxygen consumption. However, these patients did manifest a decrease in coronary sinus pO_2 as well as a decrease in lactate and pyruvate extraction. The latter measures indicate that the myocardium was functioning under hypoxic conditions. Because the coronary flow could not increase and because the myocardium could not extract O_2 from HbO_2 which was under the influence of CO, coronary sinus oxygen tension decreased to a point which could inactivate certain oxidative enzyme processes. Thus, the myocardial function of persons with CHD may be unable to compensate for the stresses induced by smoking.

Although COHb levels resulting from the CO present in the atmosphere during periods of high air pollution are much lower than those due to the inhalation of cigarette smoke, these concentrations of COHb might contribute to the manifestations of CHD. Cohen, et al. (*44*) studied the case fatality rates for patients admitted to 35 Los Angeles area hospitals with myocardial infarction in relation to atmospheric CO pollution. The authors observed an increased MI case fatality rate in areas of increased pollution, and then only during periods of relatively increased CO pollution.

An area of interest which has been discussed in previous reports concerns the presence of hydrogen cyanide in tobacco smoke. According to Wynder and Hoffmann (*215*), the amount present ranges from 11 to 32 micrograms HCN per puff. It is known that a significant amount of this material is detoxified to thiocyanate and excreted as such in the urine or saliva. However, cyanide is a potent inhibitor of oxidative metabolism. Such inhibition of myocardial oxidative metabolism may be of importance when combined with the other factors mentioned above which tend to decrease the oxygen supply available and increase the need for oxygen on the part of the myocardium.

Effects of Smoking on the Formation of Atherosclerotic Lesions

A number of autopsy studies have demonstrated a significant association between cigarette smoking and the presence of aortic and coronary artery atherosclerosis, even in men without a history of clinical CHD. The possible pathophysiologic mechanisms for the atherogenic influence of cigarette smoking are discussed in this section.

A number of investigators have studied the effect of nicotine administration, either subcutaneously or intravenously, upon atherosclerotic changes in the aorta and coronary arteries of animals (table A 23). When administered alone, nicotine induces certain necrotic changes in the arterial wall. However, in combination with the administration of increased amounts of cholesterol in the diet, nicotine aggravates either subendothelial fibrosis (*75*) or definite atheromatous lesions (*46, 75, 80, 130, 178*). Studies by Choi (*42*) and by Wenzel, et al. (*207*) did not demonstrate this synergism between cholesterol and nicotine.

The other major cigarette smoke component under discussion in this chapter, carbon monoxide, has also been recently implicated in atherogenesis. Table 24 presents the studies which have related exposure to CO in combination with increased dietary cholesterol to both macroscopic and microscopic aortic and coronary atheromatosis. Astrup, et al. (*10*) exposed cholesterol-fed rabbits to CO continually over a period of up to 10 weeks. The experimental group showed increased aortic atheromatosis over that shown by the control group, also cholesterol-fed. Kjeldsen, et al. (*114*) observed that exposure of rabbits to increased oxygen concentrations significantly reduced the amount of cholesterol-induced atheromatosis in rabbits. Most recently, Webster, et al. (*204*) have extended this research to primates. These investigators found that cholesterol-fed squirrel monkeys developed significantly more coronary artery atherosclerosis when exposed intermittently to CO over a 7-month period than when exposed only to room air.

Recent discussion has centered on the mechanisms whereby CO can induce these changes (*9, 212*). Astrup (*9*), referring to previous experiments in humans which had shown increased vascular permeability for albumin upon chronic exposure to CO (*11*), considers it likely that this increase in permeability allows for increased filtration of lipoproteins into arterial walls. This, he considers, is a primary cause of intimal and medial lipid accumulation and, therefore, of atherosclerosis.

Another point of view has been stressed by Whereat (*212*), who considers the filtration theory to be an inadequate hypothesis for

TABLE 24.—*Experiments concerning the atherogenic effect of carbon monoxide exposure and hypoxia*

Author, year, country, reference	Number and type of animal	Procedure	Results
Astrup et al., 1967 Denmark (*10*).	24 female albino rabbits.	Regular diet plus 2 percent cholesterol: I. (12) control. II. (12) continual exposure to carbon monoxide: 0.017 percent for 8 weeks. 0.035 percent for 2 weeks.	The experimental group exposed to carbon monoxide showed increased macro- and microscopic aortic atheromatosis over that shown by control animals. Microscopic examination revealed intimal lipoid deposition limited in penetration by the internal elastic membrane. Coronary vessels were found to show similar changes. Carboxyhemoglobin (COHb) levels averaged 15–19 percent during the first 8 weeks and 33 percent during the final 2 weeks.
Kjeldsen et al., 1968, Denmark (*117*).	24 castrated male albino rabbits.	Regular diet plus 2 percent cholesterol: I. (12) control. II. (12) continual exposure to hypoxia: 10 percent O_2 for 6 weeks. 9 percent O_2 for 2 weeks.	The experimental group exposed to hypoxia showed increased macroscopic aortic atheromatosis over that shown by control animals. Microscopic examination revealed more intimal and subintimal lipid deposition in the aortas of the exposed rabbits than in those of the nonexposed. The total amount of cholesterol deposited in the aortas of the experimental group was three times higher than in those of the control group.
Kjeldsen et al., 1969, Denmark (*114*).	24 castrated male albino rabbits.	Regular diet plus 2 percent cholesterol: I. (12) control. II. (12) exposure to 28 percent O_2 for 10 weeks.	Macroscopically, the experimental group showed significantly fewer atheromatous changes. Microscopically, the experimental group showed significantly less aortic intimal lipid deposition.
Webster et al., 1970, U.S.A. (*204*).	22 female squirrel monkeys.	Diet containing 0.5 percent cholesterol and 25 percent fat: I. (10) control. II. (12) experimentally exposed to 200–300 p.p.m. carbon monoxide for 20 hours per week for 7 months.	The experimental group exposed to carbon monoxide showed a greater mean percentage of coronary arteries with atherosclerotic lesions and more lumen occlusion among the affected arteries. There were significantly more CO-treated monkeys than control monkeys having 35 percent or more apparent atherosclerotic stenosis among the affected arteries. Aortic atherosclerosis was apparently not aggravated by exposure to CO. COHb levels at the end of each exposure period averaged 16–26 percent during the final 24 weeks of the experiment.

mural lipid accumulation. The author notes that when the oxidation of the pyridine nucleotide, nicotinamideadenine dinucleotide (NAD), is impaired, the reduced form of this nucleotide (NADH) provides an essential factor for fatty acid synthesis. Fatty acid synthesis in the aorta and heart is carried out by mitochondrial enzymes whose hydrogen donor is NADH. Substances which slow or impair the reoxidation of this compound tend to increase mitochondrial fatty acid synthesis (and decrease fatty acid utilization) in the arterial wall. Carbon monoxide prevents this oxidation process both directly and indirectly. Indirectly, it decreases the oxygen available for diffusion into the tissue. Directly, carbon monoxide can stall the process of NADH oxidation by combining with cytochrome oxidase. Further research is required into this problem, particularly in view of the fact that cyanide is also a respiratory chain inhibitor and thus may also adversely affect arterial wall fat metabolism.

The Effect of Smoking on Serum Lipid Levels

In the discussion concerning the epidemiological aspects of CHD, it was noted that increased serum cholesterol was a significant risk factor for the development of overt CHD. Serum triglycerides have also been related to CHD incidence. Of concern also is the immediate effect which cigarette smoking has upon blood lipid levels.

The studies concerning this immediate effect are presented in tables A 25 and A 25a. The table is divided into a section concerning studies on humans (table A 25) and one concerning studies utilizing animals or *in vitro* systems (table A 25a). Although no consistent response was noted for serum cholesterol, serum free fatty acids were found consistently to rise following smoking. As with other cardiovascular reactions to nicotine and smoking, it appears that the fatty acid response is also mediated by catecholamine release. This relationship has been observed in a number of experiments by Kershbaum, et al. (*105, 106, 108, 109, 110*) and Klensch (*118*). That nicotine is primarily responsible for this rise may be seen by reference to the study by Kershbaum, et al. (*105*) in which lettuce-leaf cigarettes of minimal nicotine content had a negligible effect upon serum free fatty acids in comparison with that of regular cigarettes.

While attention has been centered upon nicotine as the agent inducing the immediate increase in serum lipids, recent studies have been concerned with the effect of chronic exposure to carbon monoxide on serum lipid metabolism. These studies are listed in table A 26. Among rabbits fed increased amounts of cholesterol,

the authors observed significant increases in cholesterol and triglyceride concentrations in those exposed to CO versus those maintained in a normal atmosphere.

The Effect of Smoking on Thrombosis

In the study of CHD, a number of investigators have turned their attention to thrombosis because myocardial infarction and sudden coronary death frequently result from thrombotic events. A thrombus may be of either gross or microscopic dimensions, and a minute thrombus at a strategic site may precipitate a fatal arrhythmia. However, thrombotic and prethrombotic states are difficult to detect except when gross, and the emphasis has been primarily on factors which can be studied conveniently. Coagulation is now thought to have a secondary role in the consolidation of an arterial thrombus and little if any in initiating the process. The prime mechanism in thrombogenesis appears to be the reaction of the platelet. Several papers have been written about platelet reactivity *in vitro* but few about the effect of smoking on platelet behavior *in vivo*. The assay of fibrinolysis, which may also be important, has received scanty treatment. The relevant studies are listed in table A27. Many of these are discussed in the 1968 supplement (*192*) and by Murphy (*140*). Corroborative data are still inconclusive as to whether smoking shortens platelet survival.

Other Areas of Investigation

Certain other aspects of cardiovascular pathophysiology may be of importance in the relationship of smoking to CHD. Glucose metabolism and insulin response, when altered, may alter myocardial response. This topic has been covered in detail in the 1968 Supplement to the Health Consequences of Smoking (*192*). Also, variations in blood hemoglobin and hematocrit may adversely affect coronary blood flow. A number of studies showing a possible relationship of smoking to hemoconcentration have been reviewed previously (*191, 192*), and the reader is referred to those discussions.

Cerebrovascular Disease

The term cerebrovascular disease (CVD) refers to a number of different types of vascular lesions affecting the central nervous system: subarachnoid hemorrhage, cerebral hemorrhage, cerebral embolism, and thrombosis (ICD Codes 330 to 334). In 1967 in the United States, a total of 93,071 males and 109,113 females were listed as dying from CVD as the underlying cause (*196*).

Epidemiological studies indicate that cigarette smoking is asso-

ciated with increased mortality from cerebrovascular disease, whether CVD is listed as the underlying or as a contributory cause of death. Table 28 presents the results of the seven major epidemiological studies. The smoking of pipes and cigars does not appear to increase significantly the risk of dying from CVD. The importance of high blood pressure and diabetes as risk factors for mortality from CVD has recently been noted by Hammond and Garfinkel (*76*). The data from their study, as presented in table 28, also indicate that the mortality ratio for cigarette smokers is greater for persons under 75 years of age than for older individuals.

Many of the pathophysiological considerations discussed in the sections concerning CHD may also pertain to the relationship of smoking and CVD, particularly cerebral infarction.

In a study reported by Kuhn (*123*), 20 habitual smokers refrained from smoking for one-half day, and base line retrograde brachiocerebral angiograms were taken; they then smoked one cigarette, inhaling deeply, and had repeat angiograms. Those over 60 years of age failed to have significant acceleration of flow as demonstrated in carbon dioxide inhalation experiments.

More recently, Miyazaki (*132*) studied the effect of smoking on the cerebral circulation of 12 moderate/heavy cigarette smokers as measured indirectly using an ultrasonic Doppler technique to record internal carotid artery flow. Measurements were made before and after ordinary smoking and showed an increase in cerebral blood flow and a decrease in cerebral vascular resistance in all subjects. No significant difference in response was observed between the 4 younger and 8 older (over 60 years of age) subjects. More research is needed to clarify the role of cigarette smoking in the acute pathogenesis of CVD manifestations. However, the chronic effect of smoking upon the cerebral circulation (particularly its extracranial portion) is likely to be similar to the effect of smoking upon the aortic and coronary atherosclerosis.

NON-SYPHILITIC AORTIC ANEURYSM

Aortic aneurysm is an uncommon but not rare cause of death. In 1967 in the United States, a total of 8,448 men and 3,173 women were listed as dying from aortic aneurysm as the underlying cause (*196*). Cigarette smoking appears to increase the risk of dying from this disease, perhaps by promoting the atherosclerotic process which underlies this type of aneurysm. As illustrated in table 29, the mortality ratios for cigarette smokers are high relative to other cardiovascular diseases in which smoking increases the risk, and the risk increases in proportion to the amount smoked.

TABLE 28.—*Deaths from cerebrovascular disease related to smoking*

(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 due to CVD as underlying cause	Cigarettes per day	Pipes and cigars	Age variation	Comments
Hammond and Horn, 1958, U.S.A. (*77, 78*).	187,783 white males in 9 states 50–69 years of age.	Questionnaire and follow-up of death certificate.	8½	1,050	NS .....1.00 (184) Cigarettes SM .....†1.80 (556) Other SM ..1.25 (330) *Cigarettes only* <10 .....1.24 (41) 10–20 .....1.44 (140) >20 .....1.46 (83)			†($p<0.01$).
Doll and Hill, 1964, Great Britain (*80*).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	605	NS .....1.00 All SM .....1.05 All cigarette 1.12 1–14 .....1.10 15–24 .....1.09 >25 .....1.26			
Kannel et al., 1965 U.S.A. (*96*).	5,127 males and females 30–59 years of age.	Medical examination and follow-up.	12	13	NS .....1.00 (5) Heavy SM (>20) 3.23 (8)			Data apply *only* to males 30–59 years of age at entry. Data apply *only* to cerebral infarction.

[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.

TABLE 28.—*Deaths from cerebrovascular disease related to smoking (cont.)*

(Mortality ratio—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 due underlying to CVD as cause	Cigarettes per day	Pipes and cigars	Age variation	Comments
Kahn, 1966, U.S.A. (*33*).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	2,008	NS .....1.00 (614) All current ....1.80(1,894) Current cigarettes ..1.52 (692) 1-9 .....1.51 (98) 10-20 .....1.42 (825) 21-39 .....1.70 (215) >39 .....1.59 (87)	*Pipes* SM ..1.06 (82) NS ..1.00(614) *Cigars* NS ..1.00(614) SM ..1.08(185)		
Hammond and Garfinkel, 1969, U.S.A. (*76*).	358,534 males 445,875 females 40-79 years of age at entry.	Questionnaire and follow-up of death certificate.	6	4,099			*Current regular cigarette* 40-49 50-59 60-69 70-79 *Males* Never smoked 1.00 1.00 1.00 1.00 1-9 .....2.79 1.95 1.30 0.95 10-19 .....1.14 1.48 †1.44 0.92 20-39 .....2.21 2.03 1.62 1.22 >40 .....1.64 2.40 1.72 †0.68 *Females* Never smoked 1.00 1.00 1.00 1.00 1-9 .....1.50 1.26 1.26 0.83 10-19 .....2.60 2.70 2.15 †0.57 20-39 .....2.90 2.67 1.88 1.28 >40 .....†5.70 †3.52 — —	†Based on only 5-9 deaths.

[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.

TABLE 28.—*Deaths from cerebrovascular disease related to smoking (cont.)*

(Mortality ratios—actual number of deaths shown in parentheses)[1]

SM = Smokers. NS = Nonsmokers.

PROSPECTIVE STUDIES						
Paffenbarger, et al. 1970 U.S.A. (*144*).	3,268 male longshoremen 35–64 years of age in 1951.	Initial multiphasic screening and follow-up of death certificate.	16	67	NS and <20 .....1.00 (42) >20 .....1.15 (25)	
RETROSPECTIVE STUDY						
Paffenbarger and Williams 1967 U.S.A. (*145*).	>50,000 male University students followed up to 50 years.	Initial college entrance medical examinations with follow-up of death certificate. Controls—surviving classmates age-matched.			*Death Rates* *Cases (158)* *Controls (815)* SM ..... 45.0 31.3 ($p<0.01$) Cigarette SM >10 per day . 20.9 11.2 ($p<0.01$)	The 63 deaths from occlusive stroke contributed to the statistical significance. The 95 deaths from hemorrhagic stroke showed no statistical significance as a single group.

[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.

TABLE 29.—*Deaths from nonsyphilitic aortic aneurysm related to smoking—prospective studies*

(Mortality ratios—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 per day	Pipes	Cigars	Comments
Hammond and Horn, 1958, U.S.A. (77, 78).	187,783 white males in 9 states 50–69 years of age.	Questionnaire and follow-up of death certificate.	3½	68	NS .....1.00 (25) (expected) SM .....2.72 (68) ($p<0.005$)			
Kahn, 1966, U.S.A. (93).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	491	NS .....1.00 (58) Current cigarettes ....5.24 (234) 1–9 cigarettes/day ...2.12 (13) 10–20 .....5.53 (124) 21–39 .....5.95 (76) >39 .....7.26 (17)	NS ..1.00 (58) SM ..1.13 (8)	NS ..1.00 (58) SM ..2.06 (24)	
Hammond and Garfinkel, 1969, U.S.A. (76).	358,534 males 445,875 females 40–79 years of age at entry.	Questionnaire and follow-up of death certificate.	6	337	NS .....1.00 1–9 .....2.62 10–19 .....3.85 20–39 .....4.54 >40 .....8.00			Data apply only to males 50–69 years of age.
Weir and Dunn, 1970, U.S.A. (205).	68,153 California male workers 35–64 years of age at entry.	Questionnaire and follow-up of death certificate.	5–8	51	NS .....1.00 All .....2.64 ±10 .....2.44 ±20 .....2.88 ≧30 .....2.54			SM include ex-smokers, NS include pipe and cigar smokers.

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

PERIPHERAL ARTERIOSCLEROSIS

Peripheral arteriosclerosis represents the effects on the vasculature of the extremities of the pathophysiologic processes which produce coronary and aortic atherosclerosis. A number of studies have been concerned with smoking as a risk factor in the development of this disease. Kannel, et al. (*95*) observed, in the Framingham study, that diabetes mellitus and elevated serum cholesterol, as well as cigarette smoking, were also risk factors in the development of peripheral vascular disease.

Juergens, et al. (*92*) reviewed the records of and contacted 478 male patients with arteriosclerosis obliterans (a severe form of peripheral arteriosclerosis), who had been patients at the Mayo Clinic between 1939 and 1948. The diagnosis of this condition was based upon certain clinical criteria: the presence of intermittent claudication, the marked diminution or absence of lower extremity arterial pulsations, and objective trophic manifestations of peripheral limb ischemia. Smoking information was available on 401 patients. These patients were compared with a control group of 350 Mayo Clinic patients of similar age who showed no clinical evidence of vascular disease. It was found, for males under the age of 60, that 2.5 percent of the cases and 25 percent of the controls were nonsmokers. However, no difference was noted between the percentages of heavy smokers in each group. The authors also implicated high blood pressure and elevated serum cholesterol as risk factors in the occurrence of this disease.

Begg (*19*) noted similar findings in a study of 294 male patients with intermittent claudication who were patients at the Western Infirmary in Glasgow, Scotland. In comparing the smoking histories of 100 patients with this complaint with those of 116 healthy male controls, the author found that 1 percent of the patients and 21 percent of the controls had never smoked. A total of 42 percent of the patients smoked more than 20 cigarettes per day while only 24 percent of the controls had a similar history of heavy smoking. The author concluded that smoking, while not a prime cause of peripheral arterial disease, is a significant cofactor in its development in almost all cases. The author also noted obesity, high blood pressure, and elevated serum cholesterol as risk factors.

Schwartz, et al. (*168*) compared the prevalence of risk factors in four groups of subjects: 141 cases with arteriosclerotic disease of the lower limbs, 551 cases with coronary arteriosclerosis, 58 cases with both conditions, and finally an indefinite number of control individuals who had been hospitalized for injuries. The investigators reported that certain risk factors, including hypercholesterolemia, hypertension, and cigarette smoking, were signifi-

cant in both coronary and lower limb arteriosclerosis. The authors noted that the inhalation of cigarette smoke appeared to be an important risk factor for coronary arteriosclerosis up to age 55 while in arteriosclerosis of the lower extremities, inhalation appeared to increase the risk even in the older age groups.

Widmer, et al. (*213*) compared 277 male patients with arterial occlusion of the limbs as demonstrated by aortography or oscillography with 2,082 men demonstrated by oscillography to be free of arterial disease. The authors found that cigarette smoking, particularly heavy smoking, was significantly more frequent among the cases with arterial occlusion than among the controls. Increased beta-lipoproteins and systolic hypertension were also found to be more common among the cases.

Experimental Evidence

A number of experimenters have investigated the acute effects of smoking or nicotine upon the peripheral circulatory system. These investigators, as listed in table A30, have measured effects in terms of alterations in skin temperature and blood flow as measured by plethysmography, radioactive iodinated albumin clearance, or radiosodium clearance from the skin. The majority of these studies have shown significant decreases in peripheral blood flow and skin temperature upon smoking, particularly in persons without manifest peripheral vascular disease. The study of Freund and Ward (*68*) demonstrates the difference in peripheral vascular reactivity found between normals and patients with arteriosclerotic changes in the vessels of their extremities. The work of Strömblad (*181*) on blockade of this response with automatic system blockers indicates that the reactivity of these vessels is secondary to the local release of catecholamines. Most probably, the degenerative changes associated with this disease create a stiffening of the vessel wall and prevent rapid alteration, particularly dilatation, in response to the catecholamines liberated by smoking or nicotine.

THROMBOANGIITIS OBLITERANS

Thromboangiitis obliterans (Buerger's Disease) (TAO) is an uncommon obstructive vasculitis primarily involving the arteries and veins of the extremities. Severely affected patients may even lose their limbs secondary to ischemic changes. Much discussion has centered upon the question as to whether this disease is a clinical and pathological entity separate from peripheral arteriosclerosis. McKusick, et al. (*128*) consider it to be a distinct entity

while Eisen (*57*) concludes that TAO is the acute inflammatory phase of severe arteriosclerosis.

Clinically, it has been shown that smoking aggravates this disease and cessation of smoking frequently aids in complete or partial remission. Razdan, et al. (*153*) and Brown, et al. (*32*) found very few nonsmokers in groups of patients diagnosed as having typical TAO. A recent study from Israel (*16*) involved a case-control comparison of 46 patients with TAO and 32 matched controls. Although the controls were found to smoke less per day than the patients, this difference was not found to be statistically significant. However, 100 percent of the smoking patients and only 72 percent of the smoking controls were inhalers, a difference significant at the 0.02 level.

CARDIOVASCULAR DISEASES

SUMMARY AND CONCLUSIONS

Coronary Heart Disease

1. Data from numerous prospective and retrospective studies confirm the judgment that cigarette smoking is a significant risk factor contributing to the development of coronary heart disease including fatal CHD and its most severe expression, sudden and unexpected death. The risk of CHD incurred by smokers of pipes and cigars is appreciably less than that by cigarette smokers.

2. Analysis of other factors associated with CHD (high serum cholesterol, high blood pressure, and physical inactivity) shows that cigarette smoking operates independently of these other factors and can act jointly with certain of them to increase the risk of CHD appreciably.

3. There is evidence that cigarette smoking may accelerate the pathophysiological changes of pre-existing coronary heart disease and therefore contributes to sudden death from CHD.

4. Autopsy studies suggest that cigarette smoking is associated with a significant increase in atherosclerosis of the aorta and coronary arteries.

5. The cessation of smoking is associated with a decreased risk of death from CHD.

6. Experimental studies in animals and humans suggest that cigarette smoking may contribute to the development of CHD and/or its manifestations by one or more of the following mechanisms:

a. Cigarette smoking, by contributing to the release of catecholamines, causes increased myocardial wall tension, contraction

velocity, and heart rate, and thereby increases the work of the heart and the myocardial demand for oxygen and other nutrients.

b. Among individuals with coronary atherosclerosis, cigarette smoking appears to create an imbalance between the increased needs of the myocardium and an insufficient increase in coronary blood flow and oxygenation.

c. Carboxyhemoglobin, formed from the inhaled carbon monoxide, diminishes the availability of oxygen to the myocardium and may also contribute to the development of atherosclerosis.

d. The impairment of pulmonary function caused by cigarette smoking may contribute to arterial hypoxemia, thus reducing the amount of oxygen available to the myocardium.

e. Cigarette smoking may cause an increase in platelet adhesiveness which might contribute to acute thrombus formation.

Cerebrovascular Disease

1. Data from numerous prospective studies indicate that cigarette smoking is associated with increased mortality from cerebrovascular disease.

2. Experimental evidence concerning the relationship of smoking and cerebrovascular disease is at present insufficient to allow for conclusions concerning pathogenesis. However, some of the pathophysiological considerations discussed concerning CHD may also pertain to the relationship of smoking and CVD, particularly cerebral infarction.

Non-Syphilitic Aortic Aneurysm

Cigarette smoking has been observed to increase the risk of dying from nonsyphilitic aortic aneurysm.

Peripheral Vascular Disease

1. Data from a number of retrospective studies have indicated that cigarette smoking is a likely risk factor in the development of peripheral vascular disease. Cigarette smoking also appears to be a factor in the aggravation of peripheral vascular disease.

2. Cigarette smoking has been observed to alter peripheral blood flow and peripheral vascular resistance.

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CARDIOVASCULAR

APPENDIX TABLES

TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies*

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

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)	Controls (percent)	Comments
English et al., 1940, U.S.A. (60).	1,000 males with manifest CHD, 40 years of age. Controls: 1,000 male non-CHD patients.	Case selection from Mayo Foundation files. Controls: same year of admission age-matched.	*Age* *Percent Smokers* 40-49 .....79.7 (187) 50-59 .....71.7 (382) 60 or over .....63.8 (431) All ages 69.8	*Percent Smokers* 61.9 (302) (p<0.001) 73.9 (371) (not significant) 61.8 (327) (not significant) 66.3 (p<0.05)	
Mills and Porter, 1957, U.S.A. (131).	474 white male coronary deaths. Controls: 606 white males.	Undefined.			
			40-49 *50-59* *60-69* *70 or over*	*40-49* *50-59* *60-69* *70 or over*	
			(56) (135) (153) (130)	(216) (188) (114) (88)	
			NS 7.14 6.66 18.30 33.84	19.91 24.47 35.09 54.12	
			All cigarettes 83.93 82.23 49.02 18.44	70.83 59.94 43.86 16.47	
			Pipes, cigars 8.93 11.11 32.68 47.70	9.26 16.47 21.05 29.41	
Buechley et al., 1958, U.S.A. (33).	Males reporting CHD to California Health Survey with matched controls from same survey (included those surviving first myocardial infarction).	Questionnaire and interview.	NS .....20.4 (23) ≦20 .....61.1 (69) >20 .....18.5 (21)	NS .....42.1 (51) ≦20 .....46.3 (56) >20 .....11.6 (14)	

TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies (cont.)*

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

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)	Controls (percent)	Comments
Russek and Zohman, 1958, U.S.A. (*165*).	97 male and 3 female coronary patients. Controls: 100 healthy controls of similar age, sex, occupation, and ethnic origin.	Interviews by authors.	*Tobacco usage>30 cigarettes/day* 70 percent.	35 percent.	Patients included 89 with classical myocardial infarction and 11 with angina pectoris.
Spain and Nathan, 1961, U.S.A. (*176*).	269 males identified as having CHD by physical examination and history. Controls: 2,637/3,000 males identified as not having CHD	3,000 males in New York City interviewed and examined by medical group.	NS .....30.0 (81) <40/day .....29.0 (78) >40/day .....13.0 (33) EX .....14.0 (39) Cigar, pipe .....14.0 (38) Total .....100.0(269)	29.0 (772) 33.0 (870) 9.0 (234) (p<0.05) 14.0 (361) 15.0 (400) 100.0(2,637)	
Mulcahy and Hickey, 1967 Ireland (*35, 136*).	400 males less than 60 years of age with classical CHD. Data compared with male population consumption figures.	Interview.	*Males* NS ..... 4.50 (18) SM .....90.75(363) EX ..... 4.75 (19) Total .....100.00(400)	*Males* 18.2(110) 70.6(427) 11.2 (68) 100.0(605)	Control smoking data obtained from estimated smoking habits of Irish population of same age group.
Schwartz et al., 1956, France (*169*).	612 male patients with angina or myocardial infarction. 612 age-matched controls.	Interview, laboratory, and clinical examinations.	Average amount per day as cigarettes .....18.6 All SM .....86.0 Inhalers 59.0	15.5 (p<0.0001) 86.0 45.0(p<0.00001)	Data apply only to those under 55 years of age.

TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies (cont.)*

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

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)	Controls (percent)	Comments
Villiger and Heyden-Stucky, 1966, Switzerland (*201*).	100 cases with recent myocardial infarctions, 72 males, 28 females, 100 age-matched controls (72 male industrial employees and 28 females in hospital for other diagnoses).	Hospital history or interview.	*Males (72)* *Females (28)*	*Males (72)* *Females (28)*	These are not pure smoking classes. †($p<0.01$)
			NS 6.94 71.4	†25.0 82.1	
			Cigarettes 66.7 28.6	45.8 14.3	
			1-19 cigarettes/day 18.1 10.7	23.6 10.7	
			>20 .....48.6 17.9	†22.2 3.6	
			Cigar, pipe .....44.4 ...	27.8 ..	
			EX ..... 4.2 ...	†15.3 3.6	
Dörken, 1967, Germany (*52*).	205 males up to 44 years of age with myocardial infarction or sudden death (139 deceased, 66 living). Controls—Hamburg age-matched citizens selected randomly.	Death certificate review. Interview of patient or kin.	NS 1.0 (2)	18.4 (76)	Ex-smokers listed under nonsmokers. Smoking information available only on 193/205. These cigarette categories include mixed or cigar smokers recalculated as to number of cigarettes. No patients or controls smoked pipes exclusively.
			Cigarette Units		
			1-5 ..... 1.5 (3)	10.4 (43)	
			10-15 .....32.2 (62)	46.5 (192)	
			20-30 .....43.5 (84)	22.5 (93)	
			>35 .....21.8 (42)	2.2 (9)	
			100.0 (193)	100.0 (413)	
			(only 28 were mixed or cigar smokers)	(62 were mixed or cigar smokers)	
Dörken, 1967, Germany (*53*).	33 females up to 44 years of age with myocardial infarction or sudden death. Controls—133 females 27-44 years of age from clinic without CVD or lung cancer.	Death certificates, interviews.	*Cigarettes per day*		
			0 ..... 6.1 (2)	63.2 (84) ($p<0.001$)	
			1-5	17.3 (23)	
			6-15 .....48.5 (16)	16.5 (22)	
			20-30 .....39.4 (13)	3.0 (4)	
			>35 ..... 6.1 (2)	...	

TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies (cont.)*

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

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)	Controls (percent)	Comments
Hyams et al., 1967, Japan (*87*).	79 males surviving myocardial infarction. 157 age-matched controls hospitalized for non-CVD but include hypertensive disease.	Interviews by trained personnel.	NS .....10.1 (8) 1-9 cigarettes per day ..... 7.0 (5) 10-15 .....25.4 (18) 16-20 .....35.2 (25) 21-34 .....22.5 (16) >35 ..... 9.9 (7) All SM 100.0 (71)	21.0 (33) 10.5 (13) 33.9 (42) 25.8 (32) 17.7 (22) 12.1 (15) 100.0(124)	
Mulcahy et al., 1967, Ireland (*137*).	100 female patients less than 60 years of age admitted to hospital with CHD.	Hospital interviews.	SM .....63.0 (63) NS .....33.0 (33) EX ..... 4.0 (4) Total .....100.0(100)	45.6(261) 45.3(259) 9.1 (52) 100.0(572)	Smoking on controls obtained from statistics of smoking in Irish Republic. Sudden death not included.
Stejfa, 1967, Poland (*179*).	70 male and female patients with recent onset exertional angina pectoris, 54 controls of same age.	Direct interviews.	*Prevalence of risk factors* *Angina patients* 60.0	*Control group* 48.1(p>0.1)	Authors then followed the 70 patients for 3 years and noted that smoking significantly influenced the incidence of coronary occlusion.
Schimmler et al., 1968, Germany (*167*).	503 males with healed myocardial infarctions. 714 male controls of same age without detectable heart disease.	Hospital interviews.	NS ..... 9.0 (44) EX .....12.0 (59) Cigar, pipe .... ..12.0 (62) <19 cigarettes ....25.0(129) >20 .....42.0(209) Total .....100.0(503)	26.0(187) (p<0.001) 20.0(142) (p<0.001) 11.0 (77) 14.0(101) (p<0.001) 29.0(207) (p<0.001) 100.0(714)	

TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies (cont.)*

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

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)	Controls (percent)	Comments
Hood et al., 1969, Sweden (85).	230 males surviving early first myocardial infarction. Controls: 855 randomly selected males 50 years of age.	Interview and examination.	(230)	(855)	
			Never smoked 1.75	24.2	
			EX before infarction 1.75	19.7	
			EX after infarction 29.1	..	
			<15 cigarettes ...28.3	27.4	
			>15 cigarettes ...22.6	20.0	
			All 80.0	47.4	
			Pipe 16.5	8.8	
Jouve et al., 1969, France (91).	1,229 CHD patients: 802 males, 427 females. Controls: 743 individuals of both sexes; age, sex, and social class matched.	Interview.	43.0	13.0($p<0.0001$)	
Kastl, 1969, Germany (98).	275 male railway employees up to 65 years of age surviving myocardial infarction. 275 control employees with minor circulatory disturbances.	Interview and examination.	NS 20.0 (55)	29.8 (82)	
			2-20 cigarettes or up to 6 cigars....32.0 (88)	63.3 (82)	
			>20 cigarettes or >6 cigars. .....48.0(132)	6.9 (19)	

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

TABLE A7.—*Differences in serum lipids between smokers and nonsmokers*

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

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Gofman et al., 1955, U.S.A., (*72*).	401 male employees 20–59 years of age.	*Difference between SM and NS* Lipid: *Ages 20–29* (NS 55, SM 37) / *Ages 30–39* (NS 56, SM 67) / *Ages 40–59* (NS 17, SM 44) †Sf 0–12 ..... +59.9 p<0.001 / +19.9 p<0.05 / + 3.9 p<0.05 Sf 12–20 ..... + 9.4 p<0.001 / + 5.4 p<0.05 / − 3.5 p<0.05 Sf 20–100 ..... +20.0 p<0.025 / + 9.1 p<0.05 / + 8.5 p<0.05 Sf 100–400 ..... +15.8 p<0.025 / +12.1 p<0.05 / − 4.5 p<0.05 Cholesterol ..... +21.2 p<0.05 / + 9.0 p<0.05 / − 4.8 p<0.05	†Sf refers to Svedberg flotation units of centrifuged lipoproteins.
Thomas, 1958, U.S.A. (*185*).	521 medical students.	*Serum cholesterol mg. percent* *NS (264)* Observed/Expected / *SM (257)* Observed/Expected <250 ..... 170/157 / 149/161.6 >250 ..... 87/99.6 / 115/102.4 Chi Square Value = 5.2 p<0.025	
Dawber et al., 1959, U.S.A. (*47*).	2,253 males participating in the Framingham study 29–59 years of age.	*Serum cholesterol mg. percent* *29–44* / *45–59* NS ..... 216.1(149) / 228.3(131) All cigarettes ..... 224.8(874) / 220.5(589) <10 ..... 217.4 (75) / 229.1 (76) 10–19 ..... 221.1(134) / 230.1 (96) 20–39 ..... 225.8(551) / 227.8(350) >40 ..... 229.0(114) / 238.5 (68) Pipe and cigar ..... 214.9(128) / 227.1(166)	The authors conclude that there is evidence of a gradient of cholesterol with increasing amount of cigarette smoking in younger men.
Karvonen et al., 1959, Finland (*97*).	525 males in various occupations 20–59 years of age.	*Serum cholesterol mg. percent* *West Finland* / *East Finland* / *Helsinki* NS ..... 208.0(64) / 226.6 (39) / 235.1 (62) SM ..... 228.7(91) / 249.7(103) / 257.8(166)	The authors state that no trend was noted associating increasing amount smoked with increasing serum cholesterol, although smokers and nonsmokers did have different overall levels.

TABLE A7.—*Differences in serum lipids between smokers and nonsmokers (cont.)*

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

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Acheson and Jessop, 1961 Ireland (*1*).	221 randomly chosen pensioners 65–85 years of age.	*Mean serum cholesterol mg. percent* / *Mean Beta/Alpha lipoprotein ratio* NS ..... 214 (38) / 2.0 (36) 5 cigarettes/day ..... 201 (12) / 2.1 (11) 10 ..... 213 (34) / 1.9 (33) 20 ..... 201 (33) / 1.9 (35) >30 ..... 206 (8) / 1.8 (8)	
Bronte-Stewart, 1961, South Africa (*31*).	Approximately 600 healthy males 25–55 years of age.	*Cholesterol mg. percent* / *Beta/Alpha lipoprotein ratio* *25–39* / *40–55* / *25–39* / *40–55* †A ‡E / A E / A E / A E NS ..... 179 197 / 222 246 / 2.89 3.34 / 3.76 4.69 "Heavy" SM .. 186 223 / 204 236 / 3.82 4.40 / 4.07 5.40	No data given on numbers in each group. †A—African. ‡E—European.
Konttinen, 1962, Finland (*119*).	314 male military recruits 18–25 years of age.	*Serum cholesterol mg. percent* / *Serum phospholipids mg. percent* NS .....(145)..... 203.8 / 218.0 (Cigarettes per day) 1–10 (53)..... 206.8 / 222.3 11–19 .....(54)..... 213.1 / 224.7 >20 .....(62)..... 202.3 / 210.5	No serum lipid differences found among the various smoking groups.
Blomstrand and Lundman, 1966, Sweden (*26*).	76 monozygotic twin pairs and 87 dizygotic twin pairs obtained from Swedish Twin Registry.	I. Monozygotes discordant for smoking: Smokers showed slightly lower levels of cholesterol, triglycerides, and phospholipids than nonsmokers. II. Dizygotes discordant for smoking: Smokers showed significantly higher levels of phospholipids. No differences for cholesterol and triglycerides.	The authors conclude from the differing MZ and DZ results that constitutional factors are probably more important than smoking in determining lipid levels.

TABLE A7.—*Differences in serum lipids between smokers and nonsmokers (cont.)*

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

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Fidanza et al., 1966, Italy (*62*).	111 male prisoners 34–69 years of age.	*Serum cholesterol mg. percent* *Ages* <39 40–49 50–59 60–69 NS .. 196(12) 189(10) 176 (7) <20 cigarettes/day 208(5) 201(16) 202(13) 195(10) >20 cigarettes/day 197(5) 175 (7) 171 (7) .. *Serum triglycerides mg. percent* NS .. 84.7 71.9 85.0 <20 cigarettes/day 84.5 99.4 101.9 89.8 >20 cigarettes/day 91.0 86.0 66.7 ..	No statistically significant differences found between SM and NS.
Kedra and Dmowski, 1966, Poland (*98*).	200 clinically healthy males 20–50 years of age.	*Serum cholesterol mg. percent* NS(100) 170.2 SM 100) 224.0 } p<0.01 *Phospholipids mg. percent* 268.1 257.5 } p>0.05 *Total lipids mg. percent* 1,234.8 1,362.1 } p<0.01 *Total fatty acids mg. percent* NS(100) 797.8 SM 100) 869.9 } p<0.01 *Beta-lipoproteins percent of total lipoproteins* 43.1 49.9 } p<0.01	Serum cholesterol also noted to increase with increasing intensity and duration of smoking.
Harlan et al., 1967, U.S.A. (*79*).	657 former naval aviation cadets 48 years of age (average).	*Serum cholesterol* Found to be related to cigarette smoking p<0.05. *Serum triglycerides* Found not to be related to cigarette smoking. *Lipoproteins* Sf 0–12 related. p<0.05 Sf 20–100 unrelated. Sf 100–400 unrelated.	
Heyden-Storky and Schibler-Reich, 1967, Switzerland (*82*).	500 plant workers 30–60 years of age.	*Serum cholesterol mg. percent* *Serum triglycerides mg. percent* <10 cigarettes/day 210.0(334) 110.0 >10 cigarettes/day 260.0(166) 180.0	No statistically significant difference found between SM and NS.

TABLE A7.—*Differences in serum lipids between smokers and nonsmokers (cont.)*

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

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Higgins and Kjelsberg, 1967, U.S.A. (*83*).	5,030 male and female residents of Tecumseh, Michigan, 16–79 years of age.	*Males* / *Females* NS ..... 209.9 (360) / 210.1 (1,439) Cigarette ..... 212.5 (1,426) / 212.4 (910)	
Pincherly and Wright, 1967, England (*150*).	2,000 men participating in executive health examinations 28–70 years of age.	*Serum cholesterol mg. percent* / *Percentage with serum cholesterol >270 mg. percent* NS (677) ..... 236.2 / 19.0 Ex-smoker (388) ..... 246.0 / 28.0 1–19 cigarettes/day (424) ..... 239.2 / 24.0 >20 cigarettes/day (511) ..... 249.4 / 30.0	The authors noted that smokers showed significantly higher ($p<0.001$) serum cholesterol levels than nonsmokers.
Van Buchem, 1967, Netherlands (*199*).	918 randomly chosen males 40–59 years of age for entry into prospective study.	*Serum cholesterol* *0–209 mg. percent* / *210–249 mg. percent* / *>250 mg. percent* NS ..... 12.4 (32) / 14.0 (44) / 14.2 (41) Cigarette SM ..... 71.6 (184) / 67.8 (213) / 68.2 (197) Other ..... 16.0 (41) / 18.2 (57) / 17.6 (51)	The authors found no correlation between smoking and serum cholesterol levels.
Boyle et al., 1968, U.S.A. (*28*).	1,104 male factory employees 20–64 years of age.	*Serum cholesterol mg. percent* / *Serum Beta-lipoprotein mg. percent* NS ..... 243 (519) / 0.325 ; SM ..... 251 (576) / 0.351 ; $p<0.005$; $p<0.001$	Beta-lipoproteins were found to increase with age, but smokers had higher levels than nonsmokers at all ages.
Caganova et al., 1968, Czechoslovakia (*36*).	49 males living in youth hostel, 21.6 average age.	*Serum cholesterol mg. percent* / *Serum Beta-lipoprotein mg. percent* NS (34) ..... 188.20 / 359.80 SM (15) ..... 214.20 / 498.40 $p<0.025$; $p<0.001$ *Beta/alpha lipoprotein ratio* NS (34) ..... 1.16 SM (15) ..... 1.55 $p<0.025$	

TABLE A7.—*Differences in serum lipids between smokers and nonsmokers (cont.)*

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

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results			Comments
Modzelewski and Malec, 1969, Poland (*133*).	140 males 20–68 years of age.	*Serum-cholesterol* NS (20) $p<0.01$ Heavy smokers	*Serum Beta-lipoproteins* NS $p<0.01$ Heavy smokers	*Serum free fatty acids* NS $p<0.01$ Heavy smokers	
Kjeldsen, 1969, Denmark (*113*).	934 employees of various firms in Copenhagen.		*Serum cholesterol mg. percent*		
		NS (196)	236	$p<0.01$	
		SM (738)	247		
Pozner and Billimoria, 1970, England (*151*).	64 male and female healthy volunteers 19–30 years of age.		*Serum cholesterol mg. percent*	*Serum triglycerides mg. percent*	*Total phospholipids mg. percent*	Significant figures refer to heavy smokers as compared with nonsmokers.
		NS (20)	176.3	68.6	193.4	
		Light SM (17) (Over 7.3 cigarettes/day)	172.1	68.4	188.9	
		Heavy SM (27) (Over 22.5 cigarettes/day)	200.0 $p<0.05$	87.6 $p>0.05$	215.0 $p<0.001$	

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

TABLE A8.—*Blood pressure differences between smokers and nonsmokers*

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

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results			Comments
Dawber et al., 1959, U.S.A. (47).	1,253 male and female residents of Framingham.		*Systolic blood pressure*		No association found between systolic blood pressure and smoking.
			Ages 29–44	45–59	
		NS (149)	138.8	143.0	
		Cigarettes (874)	132.5	140.3	
		<10 (75)	134.7	144.0	
		10–19 (134)	129.4	141.6	
		20–39 (551)	132.2	138.9	
		>40 (114)	136.1	141.6	
		Pipe and cigar (128)	135.0	141.9	
Edwards et al., 1959, England (56).	1,737 male patients of general practitioners over 60 years of age.	*Proportion of males with "Hypertension" (≧200/≧100 mm. Hg.)*			
		NS	27.2 percent (151)		
		Cigarettes	20.5 percent (780)		
		Pipe	25.9 percent (341)		
Karvonen et al., 1959, Finland (97).	525 males in various regions of Finland 20–59 years of age.		*Systolic blood pressure*		No data on pipe and cigar smokers. No statistical significance noted.
			West Finland	*East Finland*	*Helsinki*
		NS	139.2 (64)	142.6 (39)	132.8 (62)
		SM	133.2 (91)	135.4 (103)	129.8 (166)
			Diastolic blood pressure		
		NS	84.7	86.8	89.6
		SM	81.9	84.1	86.8
Clark et al., 1967, U.S.A. (43).	1,859 male civil servants.		*Mean systolic blood-pressure*		*Mean diastolic blood-pressure*	Nonsmoker and smoker groups were of similar average age.
		NS (728)	137.0	($p \leqq 0.05$)	83.9	($p \leqq 0.05$)
		SM (407)	133.6		82.5	

TABLE A8.—*Blood pressure differences between smokers and nonsmokers (cont.)*

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

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results					Comments
Higgins and Kjelsburg, 1967, U.S.A. (*83*).	5,030 male and female residents of Tecumseh, Michigan, 16–79 years of age.		*Age adjusted mean systolic blood pressure*		*Age adjusted mean diastolic blood pressure*		
			Males	*Females*	*Males*	*Females*	
		NS 137.9 (360)		84.5 (1439)	136.6 (360)	82.1 (1439)	($p<0.001$)
		Cigarette ...136.4 (1426)		81.4 (910)	131.6 (1426)	79.0 (910)	
Reid et al., 1967, England (*155*).	676 male British and 625 male American postal workers 40–59 years of age.		*Mean systolic blood pressure (adjusted for difference in weight)*		*Mean diastolic blood pressure*		The author did note SM-NS blood pressure differences prior to controlling for weight, but not after such control.
			UK	*U.S.A.*	*UK*	*U.S.A.*	
		NS 128.2 (45)		124.8 (89)	79.3	81.0	
		1–14 grams 130.2 (27)		133.0 (60)	79.4	82.1	
		15–24 grams 128.5 (232)		127.7 (169)	78.5	77.3	
		>25 grams 127.9 (70)		128.1 (218)	77.5	77.1	
		All amounts 129.1 (519)		128.6 (447)	78.7	77.8	
Tibblin, 1967, Sweden (*187*).	895 males in Göteborg, Sweden, born in 1913.		*Blood pressure*	*115–145/ 75–95 (468)*	*150–170/ 100–110 (220)*	*>175/>115 (75)*	Numbers in parentheses represent total in blood pressure group. The author noted a stepwise decrease with level of blood pressure as smoking increased.
			≦110/≦70 (89)				
		NS 18.0		23.0	25.5	34.7	
		1–14 cigarettes 29.2		29.2	26.5	18.7	
		>15 cigarettes 28.1		20.9	15.5	17.3	
		Pipe and cigar 11.2		8.6	10.0	4.0	

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

TABLE A17.—*Incidence of new coronary heart disease by smoking category and behavior type for men 39–49 years of age*

(Numbers in parentheses are number of CHD cases in each subgroup)

Behavior type	Smoking group						
	Never smoked	Former cigarette smokers	Current and former pipe and cigar only	Cigarettes			Total
				1–15	16–25	26 and over	
A	[1]5.3(5)	13.8 (7)	1.3(1)	1.6(1)	15.8(15)	14.9(16)	9.3(45)
B	1.3(2)	5.1 (3)	2.2(2)	7.3(4)	3.1 (3)	4.9 (4)	3.3(18)
Total	2.9(7)	9.1(10)	1.8(3)	4.5(5)	9.3(18)	10.4(20)	6.2(63)

Source	Analysis of variance table				
	Sum of squares	d.f.	Mean square	F	P
Within cells	59.471	2,245	0.026	..	..
Regression on age	0.458	1	0.458	17.296	0.001
Between smoking groups[2]	0.504	5	0.101	3.81	0.002
Between behavior types[2]	0.329	1	0.329	12.43	0.001
Interaction	0.306	5	0.079	2.99	0.011

[1] Rates are age-adjusted annual incidence per 1,000 men.

[2] Mean squares for "between smoking groups" and "between behavior types" are each computed eliminating the general mean and the other main effect but ignoring interaction, thus yielding an estimate of each main effect unconfounded by other significant main effects.

SOURCE: Jenkins, C. D. et al. (*90*).

TABLE A18.—*Incidence of new coronary heart disease by smoking category and behavior type for men 50–59 years of age*

(Numbers in parentheses are number of CHD cases in each subgroup)

Behavior type	Smoking group						
	Never smoked	Former cigarette smokers	Current and former pipe and cigar only	Cigarettes			Total
				1–15	16–25	26 and over	
A	[1]12.4(5)	18.6(8)	21.8 (8)	16.4(5)	21.5 (9)	30.0(14)	20.4(49)
B	10.0(4)	5.1(1)	8.4 (3)	4.7(1)	21.1 (7)	19.1 (5)	12.0(21)
Total	11.1(9)	14.2(9)	14.9(11)	11.5(6)	21.3(16)	26.0(19)	16.8(70)

Source	Analysis of variance table				
	Sum of squares	d.f.	Mean square	F	P
Within cells	63.627	911	0.070	..	..
Regression on age	0.177	1	0.177	2.54	0.111
Between smoking groups [2]	0.522	5	0.104	1.496	0.188
Between behavior types [2]	0.296	1	0.296	4.24	0.040
Interaction	0.129	5	0.026	0.37	0.870

[1] Rates are age-adjusted annual incidence per 1,000 men.

[2] Mean squares for "between smoking groups" and "between behavior types" are each computed eliminating the general mean and the other main effect but ignoring interaction, thus yielding an estimate of each main effect unconfounded by other significant main effects.

SOURCE: Jenkins, C. D. et al. (*90*).

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Cardiac output	Coronary blood flow	Comments
Bellet et al., 1941, U.S.A. (*21*).	39 experiments on dogs which had undergone coronary artery ligation up to 45 days before.	Inhalation of tobacco smoke in chamber.	Definite increase.	Definite increase.			Coronary artery ligation increased the frequency of nicotine-induced severe arrhythmias; these became less evident with increasing time since ligation.
		Nicotine intravenous 0.2-1.2 mg./kg.	Definite increase.	Definite increase.			
Burn and Rand, 1958, England (*35*).	10 rabbits, 5 experimental, 5 control, isolated atria.	Experimental animals pretreated with intraperitoneal nicotine and the atria of both groups excised and perfused with nicotine.					Isolated atrial specimen showed increased rate and increased amplitude of contractions with administration of nicotine proportional to pretreatment. These reactions were blocked by reserpine, and the authors consider nicotine effects to be mediated by catecholamine release from chromaffin store in myocardium.
West et al., 1958, U.S.A. (*203*).	33 normal adult mongrel dogs.	Coronary intra-arterial nicotine: I. 0.2-2.2 μg./kg. II. 0.04-1 μg./kg.	Definite increase (systolic).				I. Myocardial contractility increased 40-90 percent in 16/15 animals tested accompanied by ST segment depression and T-wave inversion and blocked by tetraethylammonium chloride. II. Coronary blood flow increased 19 percent upon left circumflex artery injection; coronary blood flow showed no change upon left anterior descending artery injection, 64 observations on 10 dogs. (Tetraethylammonium chloride blocked CBF increase.) The authors found no evidence of coronary vasoconstriction in these healthy animals.

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Cardiac output	Coronary blood flow	Comments
Forte et al., 1960, U.S.A. (*65*).	27 observations on 8 dogs.	Intravenous nicotine up to 21.5 mg. given as 5–15 μg./kg./minute.		Definite initial increase then decrease.		No change.	No significant change in either left ventricular work or myocardial oxygen extraction.
Kien and Sherrod, 1960, U.S.A. (*112*).	21 adult dogs	Cigarette smoke under positive pressure via tracheostomy. Nicotine 20 μg./kg. intravenously. Epinephrine 5 μg./kg. intravenously.		Definite increase.	Definite increase.	Increase following increase in blood pressure and cardiac output.	Effects of cigarette smoke were duplicated by intravenous nicotine and epinephrine. During cigarette smoke inhalation, it was noted that without blood pressure or output changes, coronary blood flow did not increase and that while adverse EKG changes were noted they correlated more closely with decreased cardiac oxygen utilization than with actual cardiac work.
Travell et al., 1960, U.S.A. (*189*).	14 normal rabbits and 16 rabbits with severe cholesterol-induced atherosclerosis.	Intravenous nicotine 0.01–0.1 mg.				Definite increase in normals.	Nicotine-induced coronary blood flow and heart rate increase in the atherosclerotic animals required 10 times and 2 times, respectively, the amounts required in the normal animals.

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, coutry, reference	Number and type of population	Smoking procedure			Comments
Bellet et al., 1962, U.S.A. (*22*).	I. 10 normal dogs II. 9 dogs at varying intervals following coronary artery ligation. III. 7 dogs with varying grades of artificially-induced coronary artery narrowing.	Intravenous nicotine, 20 μg./kg./minute for 15–20 minutes.		I. 125 percent increase II. 82.5 percent increase III. 83.3 percent increase	The authors noted that: 1. The response of coronary blood flow to nicotine resembled that of anoxemia in the presence of coronary insufficiency. 2. The greater the induced coronary impairment the smaller the increment in coronary blood flow.
Leaders and Long, 1962, U.S.A. (*125*).	15 adult mongrel dogs.	Left anterior descending intracoronary injection of nicotine or norepinephrine.			Nicotine and norepinephrine both increased coronary vascular resistance and myocardial contractile force (the former measured by a constant-volume variable-pressure system). The action of nicotine was blocked by pretreatment with hexamethonium, pentolinium, reserpine, or guanethidine.
Larson et al., 1965, U.S.A. (*124*).	13 adult mongrel dogs.	Intravenous nicotine, 0.02 mg./kg./minute for 10–12 minutes.	Definite increase.	Definite increase.	Systemic vascular resistance and pulmonary artery and left atrial pressures showed biphasic responses of increase followed by decrease.

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Comments
Folle et al., 1966, U.S.A. (*64*).	7 dogs of 30 investigated (Remainder experienced catheterization failures).	I. Cigarette smoke inhalation to isolated left lower lobe and then blood perfused coronary arteries. II. Cigarette smoke to rest of lung and then blood passed to general circulation. III. Nicotine perfused directly into left coronary artery.	I. No change in coronary vascular resistance. II. 5/6 showed increase in coronary vascular resistance due, according to the author, to general sympathetic nervous system stimulation. III. 4/5 showed increase in coronary vascular resistance. The authors conclude that the cardiac effects of tobacco arise almost entirely from the extracardiac actions of smoking instead of the direct response of the heart.
Nadeau and James, 1967, U.S.A. (*142*).	26 dogs	Nicotine 0.01–10.0 μg. into sinus node artery.	Heart rate showed initial slowing (due probably to vagal stimulation) followed by acceleration (due probably to vagal paralysis and catecholamine release). No systemic blood pressure changes noted.
Romero and Talesnik, 1967, U.S.A. (*156*).	16 experiments on isolated cat heart.	Nicotine in varying doses in perfusate of coronary arteries.	Over 5 μg. of nicotine was found to produce an initial bradycardia associated with increased coronary flow, followed by prolonged tachycardia with an initial decrease in coronary blood flow followed by a prolonged increase. Pretreatment with hexamethonium or reserpine prevented both the myocardial stimulation and the increase in coronary blood flow. The authors consider the action of nicotine to be a combination of a direct vasoconstrictive effect and an indirect catecholamine-releasing vasodilating effect.
Puri et al., 1968, U.S.A. (*152*).	22 mongrel dogs	I. (14) Intravenous nicotine 50 μg./kg./minute for 3–4 minutes II. (8) Propranolol pretreatment, then 50 μg./kg./minute nicotine for 3–4 minutes	I. Nicotine produced a definite increase in the force and velocity of left ventricular contraction. II. Pretreatment with propranolol produced (relative to results of Group I): (a) A further increase in left ventricular systolic pressure. (b) A decrease in velocity of shortening. (c) A significant increase in left ventricular end-diastolic pressure. The authors conclude that propranolol probably impairs the norepinephrine-like effects of nicotine on the myocardium while enhancing its peripheral vasopressor effects.

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Comments
Balaza et al., 1969, U.S.A. (*16*).	Beagle dogs with lesions induced in myocardium by either: (1) Isoproterenol pretreatment, or (2) ligation of the anterior descending coronary artery.	I. Normals (3-6 per experiment); (a) 4 μg./kg. intravenous nicotine, (b) 40 μg./kg. intravenous nicotine. II. Experimental (3), 4 μg./kg. intravenous nicotine	I. (a) No evidence of arrhythmias; (b) A single or a few ectopic beats in 2/3 normal dogs. II. Extrasystoles noted in 2/3 animals during the first day after cessation of the arrhythmia induced by the lesion alone, but not thereafter. These and nicotine-induced arrhythmias were of a short duration.
Greenspan et al., 1969, U.S.A. (*74*).	Cardiac muscle isolated from the right ventricle of 10 adult dogs.	Nicotine 2-100 μg./cc. in Tyrode's solution perfusate.	Nicotine perfusion produced: (1) An increase in myocardial contractile force apparently independent of adrenergic innervation. (2) An increased automaticity of the Purkinje fiber system apparently due to release of catecholamines from chromaffin tissue stores. (3) A decrease in conduction velocity. The authors conclude that the latter two effects probably predispose to arrhythmia formation.
Saphir and Rapaport, 1969, U.S.A. (*166*).	88 mongrel cats	Nicotine 5–12 μg./kg. injected intraarterially to mesenteric circulation.	I. Mesenteric injection of nicotine was followed with 1-2 seconds by: (a) Increased left ventricular systolic pressure (LVSP). (b) Increased systemic resistance. (c) Enhanced myocardial performance. II. Left ventricular injection of nicotine was followed by: (a) Increased LVSP. (b) Bradycardia. (c) Enhanced myocardial performance greater than that seen in mesenteric-injected group. III. Pretreatment with phenoxybenzamine diminished the increase in LVSP while propranolol pretreatment diminished the enhancement of myocardial performance while LVSP still showed a significant increase. IV. Mesenteric sympathetic nerve section led to a diminished response. The authors conclude that the cardiovascular responses to nicotine may be neurogenic in nature with receptors distributed in certain abdominal arteries.

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Comments
Leb et al., 1970, U.S.A. (*126*).	12 mongrel dogs and CBF measured with use of Rb^{84} and digital counter.	Nicotine 100 μg./kg. for 2 minute intravenously.	Effective Coronary Flow (ECF) is that part of the total coronary flow (TCF) which is "effectively" involved in nutrient exchange. Nicotine injection was followed by: (1) 96.6 percent increase in TCF. (2) 51.1 percent increase in ECF. (3) 73.1 percent increase in myocardial oxygen consumption and analysis revealed that capillary flow increased almost proportionately to myocardial oxygen consumption whereas the increase in TCF was far in excess. (4) Definite increases in cardiac output, heart rate, left ventricular work, and aortic pressure.
Ross and Bloss, 1970, U.S.A. (*160*).	10 dogs undergoing instantaneous coronary arterial flow measurement.	Nicotine 10–100 μg. intracoronary injection.	Nicotine injection was followed by: (1) Increased contractile force. (2) Decreased myocardial contraction time. (3) Decreased time necessary to reach peak tension. (4) Decreased total stroke systolic CBF. (5) Increased total stroke diastolic CBF. (6) Increased total stroke CBF. (7) Changes similar to intraarterial epinephrine. (8) Changes blocked by pentolinium pretreatment. (9) No change in heart rate or blood pressure. The authors conclude that catecholamines released from the ventricular myocardium mediated these responses to nicotine.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Russek et al., 1955, U.S.A. (*164*).	I. 28 healthy male smokers 21–60 years of age (average 42). II. 37 male patients with overt clinical CHD 42–70 years of age (average 54), 6 were nonsmokers.	1 standard and 1 denicotinized cigarette.	I. Increase. II. Increase.	Increase. Increase.	EKG: I. 16/28 showed significant changes. II. No significant changes. BCG: I. ... II. 18/37 showed significant change.				Denicotinized cigarettes evoked changes of a lesser degree in normals and CHD subjects, but in the latter group there was no significant difference between these changes.
Bargeron et al., 1957, U.S.A. (*17*).	14 of 30 healthy adult male volunteer smokers and nonsmokers who underwent successful catheterization 18–53 years of age.	1 cigarette inhaled at intervals of 20 seconds.	Insignificant increase.	Increase.				Definite increase.	Coronary vascular resistance fell significantly. Myocardial O_2 usage underwent no significant change. Pyruvate extraction fell slightly. Authors consider lack of increase in heart rate as due to baseline apprehensive tachycardia.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Regan et al., 1960, U.S.A. (*154*).	7 males with history of EKG-proven myocardial infarction undergoing cardiac catheterization.	2 standard cigarettes in 25 minutes inhaled at minute intervals.	Definite increase.	Definite increase.			Increase.	No significant change.	Myocardial 0_2 consumption rose slightly in 3 out of 7. The author considers that the EKG changes noted on smoking are probably due less to decreased coronary, blood flow than to increased workload (oxygen need) where oxygen supply does not increase. Noted no evidence of myocardial ischemia during smoking.
Thomas and Murphy, 1960, U.S.A. (*186*).	113 clinically healthy young males.	One standard cigarette smoked at own pace.	Definite increase.	Definite increase.		Definite increase.	Definite increase.		Pulse pressure showed a decrease. Smokers responded slightly but significantly more actively than nonsmokers. BCG changes were increasingly common with increasing age, weight, and serum cholesterol.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Von Abn, 1960, Sweden (202).	The author reviews a series of experiments performed between 1944-1954.	Cigarette smoking.	Increase.		EKG: Slight ST segment depression and T-wave flattening.				EKG changes more prominent in young, clinically healthy subjects than in older, habitual smokers. Intravenous nicotine and smoking showed identical cardiovascular effects. Smoking elicited angina pectoris in a number of CHD patients.
Irving and Yamamoto, 1963, England (89).	5 normal males, 15 patients with diseases not defined, 19-66 years of age, all moderate-heavy cigarette smokers.	(a) Sham smoking.	(a) No change.	No change.		(a) No change.	No change.		Cardiac output measured by dye dilution technique.
		(b) Non-inhalation smoking.	(b) No change.	No change.		(b) No change.	No change.		
		(c) 2 standard cigarettes in 10 minutes.	(c) Definite increase.	Widened pulse, pressure.		(c) Definite increase.	Definite increase.		
		(d) Nicotine 0.6 mg. intravenously.	(d) Definite increase.	Definite increase.		(d) Definite increase.	Definite change.		

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Pentecost and Shilling-ford, 1964, U.S.A. (*149*).	I. 14 volunteers with clinical CHD, 13/14 smokers, average age 39.5.	Single cigarette smoked at own rate in 6–7 minutes.	Definite increase in all groups.	Definite increase in all groups.		I. 10 percent increase.	27 percent increase.		
	II. 5 patients with angina pectoris, all smokers, average age 43.4.					II. Intermediate change.	Intermediate change.		
	III. 14 patients with history of definite myocardial infarction, all smokers average age 54.1.					III. 8 percent decrease.	1 percent increase.		
Frankl et al., 1965, U.S.A. (*57*).	5 male and 3 female patients with healed myocardial infarction 48–69 years of age 2/8 non-smokers.	2 standard cigarettes in 10 minutes at rest and under graded exercise.	Definite increase at rest and at exercise.			No significant changes at rest or during exercise.	No significant changes at rest or during exercise.		The author contrasts this response with that seen among healthy young individuals.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Sen Gupta and Ghosh, 1967, India (*171*).	6 healthy male nonsmokers. 8 healthy male smokers. 6 patients with CHD, nonsmokers. 5 patients with CHD, smokers. 30–64 years of age.	1 untipped cigarette in 5–7 minutes.	Increase in all groups.	Increase in all groups.	No change. 6/8 showed ST changes. All showed ST and T-wave changes. All showed ST and T-wave changes.				
Aronow et al., 1968, U.S.A. (*5*).	10 male patients with classical angina pectoris. 32–59 years of age	1 standard high nicotine cigarette in 5 minutes.	Definite increase.	Definite increase.					Product of systolic blood pressure and heart rate showed a significant increase on smoking while left ventricular ejection time values did not. All patients developed angina more rapidly under a constant exercise load if they had smoked before exercising.
Kerrigan et al., 1968, U.S.A. (*102*).	24 male and 1 female healthy smokers, average age, 45. 8 male and 2 female healthy nonsmokers, average age 33.	2 filtered cigarettes in 15 minutes with measures taken at rest and during exercise.	Definite increase under rest and exercise conditions.	Definite increase under rest and exercise conditions.			Cardiac index. Definite increase under rest and exercise conditions.		The increase in cardiac index, heart rate, and blood pressure during exercise with smoking was the sum of such increases seen with smoking or exercise separately. Neither group showed increases in peripheral vascular resistance.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Allison and Roth, 1969, U.S.A. (*5*).	30 healthy male subjects. 19–59 years of age.	2 standard cigarettes smoked in 12–16 minute period.	Definite increase.	Increase.			Increase followed by decrease within 20 minutes.		Definite decrease in pulmonary blood volume as indicated by impedance methods of thoracic pulse volume.
Aronow and Swanson, 1969, U.S.A. (*7*).	10 male patients with classical angina pectoris. 32–59 years of age.	1 low nicotine cigarette in 5 minutes.	Definite increase.	Definite increase.					All patients developed angina sooner if they smoked before exercising.
Aronow and Swanson, 1969, U.S.A. (*6*).	10 male patients with classical angina pectoris. 32–59 years of age.	1 non-nicotine cigarette in 5 minutes.	No change.	No change.					No difference noted in time or onset of exercise-induced angina between smoking and non-smoking procedures.
Marshall et al., 1969, U.S.A. (*129*).	42 normotensive healthy male prisoners 18–50 years of age. 13 nonsmokers. 16 moderate smokers. 13 heavy smokers.	3/4 of one standard cigarette.	Insignificant increase.	Insignificant increase.					Blood pressure response to cold pressor test noted to be greater in heavy smokers. Presyncopal reactions to 40 degree head-up tilt more frequent in smokers.

TABLE A22.—*Experiments concerning the effect of nicotine or smoking on catecholamine levels*

Author, year, country, reference	Number and type of subject	Procedure	Results
Watts, 1960, U.S.A. (*203*).	11 dogs	0.02–0.60 mg/kg. nicotine intravenously.	Nicotine administration was associated with significant increases in peripheral arterial epinephrine levels. Ganglionic blocking agents prevented this effect.
Westfall and Watts, 1963, U.S.A. (*210*).	22 mongrel dogs	Cigarette smoking via tracheal cannula; 1 cigarette/8 minutes for 35 minutes.	Regular cigarette smoke evoked a statistically significant increase in adrenal vein, vena cava, and femoral artery levels of epinephrine. Cornsilk cigarette smoke evoked no change.
Westfall and Watts, 1964, U.S.A. (*211*).	21 male volunteers approximately 25 years of age; 11 nonsmokers, 10 smokers.	3 cigarettes smoked in 30 minutes.	Smoking at rate noted for 2½ hours evoked a significant increase in urinary epinephrine, but not norepinephrine levels.
Westfall et al., 1966, U.S.A. (*209*).	Mongrrel dogs	Standard cigarette smoke exposure via endotracheal tube. Smoke inhalation every third inspiration for 3 minutes.	Smoke inhalation evoked a rise in cardiac output, stroke volume, blood pressure, and plasma catecholamine levels. Pretreatment with propranolol diminished the cardiac output and stroke volume responses but increased the blood pressure response—the latter effect due to the release of alpha-receptor activity by beta-blockade.

TABLE A23.—*Experiments concerning the atherogenic effect of nicotine administration*

Author, year, country, reference	Number and type of animal	Procedure	Results
Adler et al., 1906, U.S.A. (*1*).	Rabbits	Nicotine 1.5 mg. intravenously in 5 percent solution 6 of 7 days per week for more than 4 months.	The authors noted an arterionecrosis of the aorta, affecting mainly the inner muscular layers. Macroscopically, early changes consisted of small areas of calcareous ridging and aneurysmal dilatation without notable fatty degeneration or intimal discontinuity. Microscopically, early changes appeared in the muscle cells of the media, and "chalky" deposits were noted between the elastic fibers.
Hueper, 1943, U.S.A. (*86*).	I. 6 mongrel dogs.	Nicotine subcutaneously. Increasing dosage up up to 2.5 cc. of 3 percent solution for 1 month.	I. 4/6 animals died of infection and showed marked edema and focal hyalinization of the media of the aorta and large elastic arteries. 2/6 animals were sacrificed and showed thickening and hyalinization of the walls of the coronary arteries and edema of the media as well as endothelial proliferation of other arteries.
	II. 60 rats.	Increasing doses up to 1 cc. of 1 percent solution for 1 month.	II. Much less aortic involvement than that found in the dogs; infrequent arteriolar changes consisting of fibrosis and thickening of the media.
Maslova, 1956, USSR (*130*).	Rabbits	I. (10) Nicotine subcutaneously 1 percent solution 0.2 cc. daily for 115 days.	I. Aortic wall—acute swelling of elastic fibers with *focal fragmentation* and partial disintegration—no intimal fat deposits seen. Coronary vessels—thickening of the vessel wall—no fat deposits.
		II. (14) Nicotine plus 0.2 grams cholesterol per day.	II. Aorta—"massive" deposits of "cholesterol" in the intima and vasa vasorum with "loosening" of the aortic wall. Coronary vessels—the larger vessels showed moderate fat deposition and the smaller vessels showed swelling of the elastica.
		III. (10) Cholesterol only.	III. Aorta—isolated lipid deposition in the arch and ascending portions only. Coronary vessels—no fat deposition.
Czochra-Lysanowicz et al., 1959, U.S.A. (*46*).	Rabbits	I. (10) 1.0 g. cholesterol/day for 100 days.	Index of aortic lesion density (cholesterol infiltration): I. 2.5.
		II. (10) Cholesterol plus 0.0015 g. nicotine/day intravenously.	II. 3.4.
		III. (4) Nicotine only.	III. No aortic lesions noted.

TABLE A23.—*Experiments concerning the atherogenic effect of nicotine administration (cont.)*

Author, year, country, reference	Number and type of animal	Procedure	Results
Wenzel et al., 1959, U.S.A. (*187*).	Rabbits	I. (12) Control untreated. II. (12) Control diet plus 1 percent cholesterol and 5 percent cottonseed oil added. III. (12) Control diet plus oral nicotine 2.28 mg./kg./day. IV. (12) Regimen II plus oral nicotine 2.28 mg./kg./day. V. (12) Regimen II plus oral nicotine 1.42 mg./kg./day. VI. (12) Regimen II plus oral nicotine 0.57 mg./kg./day.	General findings: Marked aortic pathologic involvement was noted in all cholesterol-treated groups; however, no difference was noted between Group II. and Groups IV., V., and VI. Cardiac histopathology: I. No change. II. Advanced atherosclerotic changes in the subendocardial vessels. III. Thickening and fibrosis of coronary artery small branches. IV.-VI. More severe changes with greater fatty metamorphosis and actual early myocardial necrosis, but no dose-dependent effects observed.
Thienes 1960, U.S.A. (*184*).	Newborn rats and mice.	Nicotine subcutaneously up to 5 mg./kg. twice daily by the end of 1 month. Animals autopsied at 1 year.	No arterial pathology noted. Medial degeneration seen more frequently in controls. Suggests that older animals be used.
Grosgogeat et al., 1965, France (*75*).	Male rabbits	I. (10) Nicotine subcutaneously 0.75 mg./day. (10) Controls—saline injected. Sacrificed at from 20–120 days. II. (27) Same as Group I. (27) Controls—saline injected. Sacrificed at 90 days. III. (66) Nicotine subcutaneously 0.3–1.5 mg./day. Sacrificed at 30 days. IV. (24) Nicotine subcutaneously 0.75 mg./day. (24) Controls—saline injected. One-half of each group ate cholesterol-enriched diet (0.5–1.0 percent cholesterol added). Sacrificed at 60 days.	Significant differences in aortic subendothelial fibrosis between control and experimental groups noted only in II and IV. In group IV, the nicotine-treated group showed more severe changes.

TABLE A23.—*Experiments concerning the atherogenic effect of nicotine administration (cont.)*

Author, year, country, reference	Number and type of animal	Procedure	Results
Haas et al., 1966, U.S.A. (*80*).	Male rabbits	*Nicotine* *Diet* *Vitamin D* I. (8) Control Control Control II. (7) Control Cholesterol Control III. (14) Nicotine Control Control IV. (15) Nicotine Cholesterol Control V. (9) Control Cholesterol Vitamin D VI. (14) Nicotine Cholesterol Vitamin D (Sacrificed at various times) Control—no treatment. Nicotine—subcutaneous injections in oil—increasing amounts 2 times per week. Vitamin D—subcutaneous injections up to 6–8 x 10^5 IU. Cholesterol—250–500 mg. cholesterol added per 100 g. diet.	I. Infrequent medial calcific disease without lipid localization. II. No medial calcific disease but frequent intimal atheroma formation. III. Rare calcific medial degeneration; no intimal atheromatous disease. IV. The largest number of atheromatous lesions. V. No medial calcific disease. VI. Consistent medial calcific disease.
Choi, 1967, Korea (*42*).	Albino rabbits	I. Nicotine 1–5 mg./kg./day intraperitoneally. Cholesterol 1 g./day (in varying combinations with controls). II. Nicotine alone. III. Cholesterol alone. (Sacrificed at 60 days)	I. Increasing nicotine dosages were associated with decreased atheroma formation (findings not statistically significant). II. Nicotine alone produced no atheroma formation but was associated with the presence of aortic medial calcification and endothelial hyperplasia. III. Cholesterol alone was associated with a definite increase in atheroma formation.
Stefanovich et al., 1969, U.S.A. (*178*).	Female albino rabbits.	I. (10) Diet supplemented with 2.0 percent cholesterol. Nicotine intramuscularly 2.78 mg./kg./day, 5/7 days. II. (10) Cholesterol only. III. (10) Nicotine only. IV. (10) Control.	*Percent of aortic surface involved with atherosclerosis* I. 9.4 II. 5.7 III. 0.1 IV. ..	In both stuck and cholesterol-fed animals, nicotine was also noted to increase aortic triglyceride content and to decrease aortic free cholesterol content.

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

Author, year, country, reference	Number and type of population	Smoking procedure	Plasma free fatty acids	Serum cholesterol	Serum triglycerides	Other	Comments
Page et al., 1959, U.S.A. (*147*).	13 male and 7 female laboratory workers 17–51 years of age.	2 nonfiltered cigarettes in 10 minutes and blood levels measured over 30-minute period.		No change.		*Serum lipoproteins* No change (10 subjects).	
Kershbaum et al., 1961, U.S.A. (*104*).	31 male patients or staff 16–72 years of age, 7 normals, 7 CHD, 17 other medical diagnoses.	I. 17 subjects smoked 2 non-filter cigarettes in 10 minutes. II. 9 controls. III. 5 subjects smoked 6 cigarettes in 40 minutes.	*Mean rise* I. 351 μEq./L. II. 9.8 μEq./L. III. 272–2,304 μEq./L.	No change.	No change.		The authors consider the increase among controls to be due to fasting.
Kershbaum et al., 1962, U.S.A. (*103*).	I. 17 male patients with healed myocardial infarctions. II. 16 non-CHD patients. III. 10 normals. IV. 13 normals.	I., II., III., 2 non-filter cigarettes in 10 minutes. IV. No smoking.	*Mean rise* I. 858 μEq./L. II. 320 μEq./L. III. 292 μEq./L. IV. 20 μEq./L.				No difference found between results following inhalation or noninhalation. Statistically significant difference found between increases in Groups II and III and Group I.

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

(Human Studies)

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Smoking procedure	Plasma free fatty acids	Serum cholesterol	Serum triglycerides	Other	Comments
Kershbaum et al., 1963, U.S.A. (*189*).	11 normal patients.	9 standard cigarettes in 3 hours. Samples at 10, 20, and 40 minutes of smoking period.	Definite increase at start of smoking period.			3 patients with trimethaphan camphorsulfonate (Arfonad) pretreatment and 8 formerly adrenalectomized patients showed either minimal or no elevation.	Both free and total urinary catecholamines increased with smoking and the author considers them as mediators of the FFA increase.
Konttinen and Rajasalmi, 1963, Finland (*120*).	40 healthy moderate smokers 19–20 years of age.	Fed at fat meal and then 20 were allowed to smoke cigarettes of known-nicotine content over 6 hour period (approximately 23 cigarettes consumed).	NS—definite increase at 6 hours. SM—definite increase at 6 hours.	No change in either group.	NS—definite increase at 2 hours. SM—slight increase at 2 hours.		
Kedra et al., 1965, Poland (*101*).	37 male and 5 female medical students 22–23 years of age.	3 cigarettes smoked in rapid succession and samples taken at 10 and 30 minutes.	No change.	No change.		Beta-lipoproteins definite increase.	

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
Frankl et al., 1966, U.S.A. (*66*).	5 male and 1 female healthy smokers 24–29 years of age.	2 standard cigarettes inhaled in 10 minutes.	No change.				Subjects were in nonfasting, nonbasal state.
Kershbaum et al., 1966, U.S.A. (*106*).	43 normal male heavy cigarette or cigar smokers, 21–46 years of age.	I. Terminal segment of cigar in 20 minutes—15 subjects. II. 3 cigarettes in 20 minutes 15 subjects (including 6 from group I). III. Cigarette inhalation or noninhalation 6 subjects.	I. Indefinite increase. II. Definite increase. III. Increase with inhalation greater than with non-inhalation in every subject.				Cigar smoking in 11 subjects showed an intermediate increase in the excretion of urinary catecholamines as compared to that with cigarette smoking.
Klensch, 1966, Germany (*118*).	56 observations on student smokers 20–24 years of age.	1 standard cigarette in 4 minutes. FFA measured at 16–25 minutes.	Definite increase.				Indefinite increase in venous epinephrine levels.

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. (*205*).	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 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. (*104*).	6 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 resulting 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 to 0.020 percent CO for 7 weeks, then 0.036 percent CO for 3 weeks.	I. Serum cholesterol concentrations rose rapidly 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 [1]	Whole blood clotting time	Prothrombin 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 styptven 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 male nonsmoking medical students <30 years of age.	Deep inhalation of one nonfiltered cigarette.	(−)		(−)	(−)	(±) increase	(−)			*Thromboplastin 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 $p < 0.01$.

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

Author, year, country, reference	Number and type of population	Experimental conditions	Whole blood clotting time	Prothrombin time	Partial thromboplastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Sognal and Joshi, 1955, 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	Biri—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 Koroliko, 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 [1]	Whole blood clotting time	Prothrombin time	Partial thromboplastin 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 serotinin* (–) *Platelet adenosine nucleotide* (–)	Smokers found to have a greater tendency for platelet aggregation than nonsmokers.
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. (*140*).	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.

[1] 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. (*154*).	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. (*158*).	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. (*79*).	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.
Stromblad, 1959, Sweden (*131*).	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. (*151*).	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 2

Cardiovascular Diseases

Part II

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CORONARY HEART DISEASE (CHD)

Introduction

Coronary Heart Disease (CHD) is the most frequent cause of death in the United States and is the most important single cause of excess mortality among cigarette smokers. The evidence relating smoking to CHD has been reviewed in previous reports on the health consequences of smoking (*61, 62, 63, 64, 65, 66, 67, 68*). The following is a brief summary of the relationships between smoking and CHD presented in these reports.

Cigarette smoking, hypertension, and elevated serum cholesterol are the major alterable risk factors for myocardial infarction and death from CHD. Cigarette smoking acts both independently as a risk factor and synergistically with the other CHD risk factors. The magnitude of the risk increases directly with the amount smoked. The excess risk of CHD among smokers has been demonstrated in some Asian, Black, and Caucasian populations and is proportionately greater for younger men, especially those below age 50. Cessation of cigarette smoking results in a reduced mortality rate from CHD compared with the mortality rate for those who continue to smoke.

Pipe and cigar smokers have a slightly higher risk of death from CHD than nonsmokers, but they incur a much lower risk than cigarette smokers. This has been attributed to the lower levels of inhalation that characterize most pipe and cigar smoking.

Data from autopsy studies have shown coronary atherosclerosis to be more frequent and more extensive in cigarette smokers than in nonsmokers, and experimental work in humans and animals has suggested several mechanisms by which smoking may influence the development of atherosclerosis and CHD. The formation of carboxyhemoglobin, release of catecholamines, creation of an imbalance between myocardial oxygen supply and demand, and increased platelet adhesiveness leading to thrombus formation have all been demonstrated in smokers and proposed as explanations for the excess CHD mortality and morbidity among smokers.

Cigarette Smoking as a Major Risk Factor for Coronary Heart Disease

The evidence establishing smoking as a major risk factor in CHD has been reviewed in previous reports (*61, 62, 63, 64, 65, 66, 67, 68*). During the last year new epidemiologic data have been published on the relationship between coronary artery disease and smoking.

Bengtsson (*9, 10*) studied the smoking habits of women with myocardial infarction (MI) in Goteborg, Sweden. He found that smoking was significantly more common in a group of 46 women (80 percent smokers), ages 50-54, who had a myocardial infarction than in a control group of 578 healthy nonhospitalized women (37.2 percent smokers).

Other investigators examined the effect of cigarette smoking on survival of people with acute myocardial infarction. In a study of 400 patients with documented myocardial infarction who survived to be admitted to a coronary care unit, Helmers (*26, 27, 28*) found no significant difference between the percentages of smokers and nonsmokers among survivors studied after the first 24 hours, from 2 days until discharge, and from discharge to 3 years. Reynertson and Tzagournis (*52*), in a 5-year prospective study of 137 patients with documented CHD at age 50 or less, were also unable to find any relationship between CHD mortality rates and smoking habits. Smoking habits after entrance into the study were also considered and again no difference in mortality rates was found.

The Coronary Drug Project (*17*) found an effect of cigarette smoking on mortality after myocardial infarction. This group studied 2,789 men ages 30-64 years for 3 years after myocardial infarction and found a statistically significant correlation between cigarette smoking determined 3 months after a myocardial infarction and mortality (t-value of 2.94). None of these studies (*17, 26, 27, 28, 52*) were able to examine the smoking habits of the group of people who die suddenly as a first manifestation of CHD, and therefore may have excluded that group in which there is the highest excess mortality due to cigarette smoking (*31*).

Additional data from the Swedish twin study of Friberg, et al. (*23*) have been reported. They found an excess CHD mortality among smokers in dizygotic twins with different degrees of smoking, but no similar excess in monozygotic twins. Although the numbers were too small to be significant, the authors suggest that this tends to support the theory that both smoking and CHD are constitutionally

determined. These data must be viewed with caution, however, since the difference was demonstrable only in the older age group (born 1901 - 1910). When the younger age group (born 1911 - 1925) was considered, no excess CHD mortality was seen in the dizygotic group but a small excess was noted in the monozygotic group (three CHD deaths in the high smoking group and one in the low smoking group). Also the difference in cigarette consumption between the high and low smoking groups was relatively small (seven cigarettes per day). Consequently, data from this study are not sufficient to warrant the conclusion that both smoking and excess CHD mortality are constitutionally determined rather than smoking being a cause of the excess CHD mortality.

Cigarette Smoking in Relation to Other Risk Factors for Coronary Heart Disease

Cigarette smoking, elevated serum cholesterol, and elevated blood pressure are generally accepted as the three major modifiable risk factors for CHD. However, there is less agreement concerning other CHD risk factors – obesity, physical inactivity, diabetes mellitus, elevated resting heart rate, psychologic type A behavior, etc. The following studies present recent evidence on the relationships between smoking and hypertension, coffee drinking, and ventricular premature beats.

Hypertension

Results from several studies have shown that smokers on the average have slightly lower blood pressure than nonsmokers. Some investigators have attributed this finding to the fact that smokers on the average weigh slightly less than nonsmokers. Three current studies (*24, 36, 55*) discuss this relationship. Gyntelberg and Meyer (*24*), based on their evaluation of 5,249 men ages 40-59, were of the opinion that lower blood pressure in smokers could not be accounted for by differences in weight, age, or physical fitness. Kesteloot and Van Houte (*36*), in a study of 42,804 men, performed a multiple regression analysis on age, weight, and height and found that cigarette smokers had lower blood pressure than nonsmokers; however, when they included serum cholesterol values in the analysis, the difference in blood pressure was reduced to approximately 1 mm Hg. Although this difference was statistically significant based on the large population, the actual difference in blood pressure was too small to be of clinical importance.

Seltzer (*55*) studied 794 men selected for their initial good health and normal blood pressure (below 140 systolic and 90 diastolic) and followed them for changes in cigarette smoking habits, weight, and blood pressure. During the 5-year period of the study 104 men gave up smoking. For every age group except those over 55, there was a significantly greater weight gain (8 lb) among the "quitters" than among the continuing smokers (3.5 lb). Blood pressure increased 4 mm Hg systolic and 2.5 mm Hg diastolic in the quitters with no change in systolic and a slight reduction in diastolic (-1.1 mm Hg) in persons who continued to smoke. In order to examine blood pressure changes in relation to weight change, both continuing smokers and quitters were grouped according to their weight changes during the period of study (Table 1). The most significant finding was an increase in the systolic blood pressure (+1.77 mm Hg) among the quitters even in that group with significant weight loss. In contrast, the continuing smokers with significant weight loss had a decline in systolic blood pressure (-3.28 mm Hg). Diastolic blood pressure in quitters showed an increase with weight gain and no change with weight loss, while continuing smokers showed a decrease in diastolic pressure with weight loss and no change with weight gain. The data on subjects whose blood pressure had increased to hypertensive levels (systolic > 150 and diastolic > 95) were evaluated, and it was found that quitters had a much higher frequency of becoming hypertensive than continuing smokers (Table 2).

Seltzer, in interpreting these data, suggested that cigarette smoking tends to inhibit blood pressure increases, with only minimal pressure rises occurring even in instances of substantial weight gain. When this inhibiting effect of cigarette smoking is removed as in the case of the quitters, sharp rises in blood pressure become evident. He cautioned, however, that the development of hypertension in some quitters may have been responsible for decisions to lose weight and that his data do not allow an evaluation of the degree of blood pressure changes according to how recently cigarettes were given up.

The results of the ischemic heart disease study by Kahn, et al. (*34*) raise additional questions about Seltzer's data. Kahn followed 10,000 Israeli male civil service employees for 5 years to determine what factors were associated with an increased incidence of hypertension. He presented no data concerning persons who stopped smoking, but he did show that the incidence of hypertension increased with age and that the age-adjusted incidence of hypertension in smokers was over twice that of nonsmokers (76.9/1000 for smokers versus 35.4/1000 for nonsmokers). Seltzer reported no

TABLE 1. – *Age-standardized blood pressure changes (mm Hg)[1] at followup for continuing cigarette smokers and quitters according to weight changes*

Smoking Class	Weight Change (LB)							
	Significant Wt Loss		No Significant Wt Change		Moderate Wt Gain		Significant Wt Gain	
	No.	lb -25 to -5	No.	lb -4 to +4	No.	lb +5 to +12	No.	lb +13 to +30
Mean systolic BP changes:								
Continuing smokers	32	−4.00	84	−1.52	71	2.85	24	1.50
Quitters	13	1.77	27	2.22	27	4.04	32	3.69
Mean diastolic BP changes:								
Continuing smokers	32	−3.28	84	−2.04	71	0.73	24	−0.04
Quitters	13	−0.31	27	−1.96	27	4.30	32	3.94

[1]Standardized on basis of age distribution of current cigarette smokers.

Source: Seltzer, C.C. (*55*).

TABLE 2. – *Number of subjects who had developed hypertension at followup for continuing cigarette smokers and quitters*

Blood pressure levels	Continuing cigarette smokers		Quitters	
	Number	Percent	Number	Percent
Systolic blood pressure 150+	6	2.8	9	8.7
Systolic blood pressure 160+	2	0.9	5	4.8
Diastolic blood pressure 95+	3	1.4	5	4.8

Source: Seltzer, C.C. (*55*).

data on the incidence of hypertension in nonsmokers, and the age distribution for his group of smokers (the original source of the quitters) is heavily weighted toward younger age groups (with only 33 of 214 men age 50 years or over). According to Kahn's data, this age group would be expected to have a lower incidence of hypertension, and, in fact, Seltzer found only small numbers of men who developed hypertension (eight with diastolic hypertension) (Table 2). Making interpretations based on such small numbers is hazardous; for example, the difference between current smokers and quitters in the incidence of diastolic hypertension could have been produced by only three men quitting smoking because they developed hypertension.

Coffee Drinking

The Boston Collaborative Drug Study (*12*) recently reported a correlation between coffee drinking ($\geq$ 6 cups per day) and myocardial infarction that persisted after controlling for the effect of cigarette smoking. This was a retrospective study of 276 patients with a hospital discharge diagnosis of myocardial infarction and 1,104 age, sex, and hospital-matched controls discharged with other diagnoses. In addition to the usual limitations of retrospective studies, this study has several characteristics that make interpretation difficult. In controlling for the effect of cigarette smoking, the investigators divided the smokers into those who smoked one pack or less per day and those who smoked more than one pack per day. Because cigarette consumption is highly correlated with coffee consumption (*29, 39*), it can be expected that within such broad smoking categories those who were heavy coffee drinkers tended to be heavier smokers than those who consumed smaller amounts of coffee. It is also possible that the hospitalized controls represented persons who drank less coffee than the general population because of serious chronic illnesses. These characteristics of the study design do not allow firm conclusions to be made concerning the extent to which the relationship between coffee drinking and myocardial infarction is independent of the relationship of both variables to cigarette smoking.

The question of the independent nature of this relationship is also dealt with in a prospective study by Klatsky, et al. (*39*) of 464 patients with myocardial infarction who previously had had multiphasic health checkups. Both ordinary controls and CHD risk factor-matched controls were drawn from 250,000 people who had undergone the same multiphasic health checkups. The investigators did not find an independent correlation between coffee drinking and myocardial infarction when risk-matched controls were used.

The Framingham Study (*18*) recently published data on coffee drinking based on a 12-year followup of 5,209 men and women ages 30-62. An increased risk of death from all causes was demonstrated in coffee drinkers, but this relationship was accounted for by the association between coffee consumption and cigarette smoking. No association between coffee drinking and myocardial infarction or between coffee drinking and the development of CHD, stroke, or intermittent claudication was demonstrated. Heyden, et al. (*29*) also found no relationship between excessive coffee consumption (> 5 cups per day) and atherosclerotic vascular disease.

Ventricular Premature Beats

Ventricular premature beats have been shown to be a risk factor for sudden death from CHD. Vedin, et al. (*69*), in a study of 793 men in Goteborg, Sweden, examined the frequency of rhythm and conduction disturbances at rest and during exercise. They found no statistically significant correlation between cigarette smoking habits and the presence of supraventricular or ventricular premature beats at rest or during exercise.

CARBON MONOXIDE

Introduction

Carbon monoxide has long been recognized as a dangerous gas, but until recently concentrations which produced carboxyhemoglobin levels below 15 to 20 percent were thought to have little effect on humans. Currently there is considerable interest in determining the effect of chronic exposure to low levels of carbon monoxide (*65, 66, 67, 68*).

Carbon monoxide is present in concentrations of 1 to 5 percent of the gaseous phase of cigarette smoke (*11, 45*). The concentration varies with temperature of combustion as well as with factors which control the oxygen supply such as the porosity of the paper and packing of the tobacco. The amount of carbon monoxide produced increases as the cigarette burns down. Carboxyhemoglobin levels in smokers vary from 2 to 15 percent depending on the amount smoked, degree of inhalation, and the time elapsed since smoking the last cigarette.

Carbon monoxide, which has 230 times the affinity of oxygen for hemoglobin, impairs oxygen transportation in at least two ways:

First, it competes with oxygen for hemoglobin binding sites. Second, it increases the affinity of the remaining hemoglobin for oxygen, thereby requiring a larger gradient in Po_2 between the blood and tissue to deliver a given amount of oxygen; this increased gradient is usually produced by a lowering of the tissue Po_2.

Carbon monoxide also binds to other heme-containing pigments, most notably myoglobin, for which it has even a greater affinity than for hemoglobin under conditions of low Po_2. The significance of this binding is unclear, but may be important in tissues, such as the heart muscle, which have both high oxygen requirements and large amounts of myoglobin.

Sources of Carbon Monoxide Exposure and Human Absorption

Several researchers (*13, 32, 35, 57, 60, 70*) have estimated the relative contribution of cigarette smoking and air pollution to the human carbon monoxide burden as measured by carboxyhemoglobin levels (COHb). Kahn, et al. (*35*), in a study of 16,649 blood donors, determined that smoking was the most important contributing factor, followed by industrial work exposure. Nonsmoking industrial workers had COHb levels of 1.38 percent, and nonsmokers without industrial exposure had levels of .78 percent. Cigarette smokers, on the other hand, had very high levels. Smokers with industrial exposure had levels of 5.01 percent, while smokers without industrial exposure had levels of 4.44 percent (Tables 3 and 4). Stewart, et al. (*57*) found similar results in a nationwide survey of blood donors and noted marked variation in mean COHb levels in residents of different cities measured at different times of the year (Table 5). However, in all areas, smokers still had COHb levels two to three times higher than nonsmokers and had increasing COHb levels with increasing level of cigarette consumption (Table 6). Similar findings were reported by Torbati, et al (*60*) in a study of 500 male Israeli blood donors.

Nonsmoking workers exposed to automobile exhaust – London taxi drivers (*32*) and garage and service station operators (*13*) – have higher baseline levels of carboxyhemoglobin than nonsmokers of the general population. But even in these high exposure occupations smokers have markedly higher COHb levels (8.1 and 10.8 percent) than nonsmokers (6.3 and 5.5 percent). An extreme is represented by New York City tunnel workers who are exposed to an average of 63 ppm CO with peak exposure levels as high as 217 ppm CO; cigarette smokers still maintained much higher COHb levels (5.01 percent) than nonsmokers (2.93 percent) (*8*).

TABLE 3. – *Mean percent of carboxyhemoglobin saturation in smokers and nonsmokers by sex and race*

	Total Sample		Nonsmokers		Smokers[1]	
	No.	$\bar{X} \pm S_{\bar{X}}$	No.	$\bar{X} \pm S_{\bar{X}}$	No.	$\bar{X} \pm S_{\bar{X}}$
Total Sample	16,649	2.30 ± 0.02	10,157	0.85 ± 0.01	6,492	4.58 ± 0.03
Male	10,542	2.66 ± 0.03	5,888	1.00 ± 0.01	4,654	4.76 ± 0.04
Female	6,107	1.68 ± 0.03	4,269	0.64 ± 0.01	1,838	4.10 ± 0.06
White	15,167	2.28 ± 0.02	9,474	0.85 ± 0.01	5,693	4.66 ± 0.04
Male	9,669	2.65 ± 0.03	5,508	1.00 ± 0.01	4,161	4.83 ± 0.04
Female	5,498	1.63 ± 0.03	3,966	0.64 ± 0.01	1,532	4.19 ± 0.06
Black	1,429	2.59 ± 0.06	641	0.86 ± 0.03	788	4.00 ± 0.08
Male	829	2.91 ± 0.10	347	1.07 ± 0.05	482	4.24 ± 0.10
Female	600	2.15 ± 0.09	294	0.62 ± 0.04	306	3.63 ± 0.12

[1]Smokers are defined as those who smoked on the day of giving blood.

NOTE. – $\bar{X}$ = mean percent; $S_{\bar{X}}$ = standard error of mean percent.

Source: Kahn, A., et al. (*35*).

TABLE 4. – *Mean percent of carboxyhemoglobin saturation in smokers and nonsmokers by employment status*

	Nonsmokers		Smokers[1]	
	No.	$\bar{X} \pm S_{\bar{X}}$	No.	$\bar{X} \pm S_{\bar{X}}$
Persons employed	8,478	0.89 ± 0.01	5,962	4.61 ± 0.03
Classed as industrial workers[1]	1,523	1.38 ± 0.04	1,738	5.01 ± 0.06
Classed as workers other than industrial	6,955	0.78 ± 0.01	4,224	4.44 ± 0.04
Persons not employed	1,678	0.63 ± 0.02	531	4.24 ± 0.11

[1]Industrial workers are employed in either durable or nondurable goods manufacturing (craftsmen, operatives, or laborers). Smokers are defined as those who smoked on the day of giving blood.

NOTE. – $\bar{X}$ = mean percent; $S_{\bar{X}}$ = standard error of mean percent.

Source: Kahn, A., et al. (*35*).

TABLE 5. – *Median percent carboxyhemoglobin (COHb) saturation and 90 percent range for smokers and nonsmokers by location*

Location	Cigarette Smokers		Nonsmokers	
	Median	Range	Median	Range
Anchorage	4.7	0.9 – 9.5	1.5	0.6 – 3.2
Chicago	5.8	2.0 – 9.9	1.7	1.0 – 3.2
Denver	5.5	2.0 – 9.8	2.0	0.9 – 3.7
Detroit	5.6	1.6 – 10.4	1.6	0.7 – 2.7
Honolulu	4.9	1.6 – 9.0	1.4	0.7 – 2.5
Houston	3.2	1.0 – 7.8	1.2	0.6 – 3.5
Los Angeles	6.2	2.0 – 10.3	1.8	1.0 – 3.0
Miami	5.0	1.2 – 9.7	1.2	0.4 – 3.0
Milwaukee	4.2	1.0 – 8.9	1.2	0.5 – 2.5
New Orleans	5.5	2.0 – 9.6	1.6	1.0 – 3.0
New York	4.8	1.2 – 9.1	1.2	0.6 – 2.5
Phoenix	4.1	0.9 – 8.7	1.2	0.5 – 2.5
St. Louis	5.1	1.7 – 9.2	1.4	0.9 – 2.1
Salt Lake City	5.1	1.5 – 9.5	1.2	0.6 – 2.5
San Francisco	5.4	1.6 – 9.8	1.5	0.8 – 2.7
Seattle	5.7	1.7 – 9.6	1.5	0.8 – 2.7
Vermont, New Hampshire	4.8	1.4 – 9.0	1.2	0.8 – 2.1
Washington, DC	4.9	1.2 – 8.4	1.2	0.6 – 2.5

Source: Stewart, R.D., et al. (57).

TABLE 6. – *Mean percent carboxyhemoglobin (COHb) saturation in cigarette smokers 1 hour after last cigarette*

Location	Nonsmoker	Packs of Cigarettes Smoked Per day				
		< ½	½-1	1	1½	2
Milwaukee	1.3	3.0	4.2	5.3	6.2	4.7
New Hampshire, Vermont	1.4	3.3	4.4	5.7	6.7	5.3
New York City	1.4	3.1	4.3	4.7	5.8	6.3
Washington, DC	1.4	3.8	4.6	5.2	5.8	6.6
Los Angeles	2.0	4.0	5.2	6.0	7.4	7.5
Chicago	2.0	4.8	5.4	6.3	7.1	7.7

Source: Stewart, R.D., et al. (57).

Studies on the CO burden of each cigarette have determined the body burden of CO per cigarette to be 7.10-8.66 ml (*40*), and the increase in COHb level produced by smoking one cigarette to be .94 to 1.6 percent after 12 hours of abstinence (*40, 53*). The half-life for the washout of CO in healthy college smokers (*40*) was calculated to be from 3 to 5 hours.

Effects on Healthy Individuals

Several studies have been published on the effects of carbon monoxide on healthy individuals. Small doses of CO (COHb levels 2.4-5.4 percent) were found to have no effect on heart rate (*56*). Raven, et al. (*51*), in a study of young men exposed during exercise on a treadmill to 50 ppm CO (COHb levels 2.5 percent in nonsmokers and 4.1 in smokers), found no decrease in maximum aerobic capacity when the subjects were tested at 25° C. In a similar experiment conducted at 35° C by the same researchers (*20*), there was a decrease in maximum aerobic capacity in nonsmokers exposed to 50 ppm CO, but not in smokers despite an increase in the carboxyhemoglobin levels of 1.5 percent in both groups. They postulated a possible physiologic adaptation of smokers to carbon monoxide. Ekblom and Huot (*22*) studied five young men who inhaled CO to reach given COHb levels. They reported that as COHb levels increased, there was a decrease in maximal oxygen uptake and lower heart rates at maximal treadmill exercise.

Sagone, et al. (*54*), in a study of 9 cigarette smokers and 18 nonsmokers ages 20-32, showed significantly higher values for COHb, red cell mass, hemoglobin, and hematocrit in the smokers. Levels of 2,3 DPG were unaltered while oxyhemoglobin affinity P50 and ATP levels were significantly lower in the smokers. The three smokers with highest red cell mass had normal arterial blood gases and one smoker had very high values of red cell mass which returned to normal after he stopped smoking. The authors interpret these data as evidence of tissue hypoxia.

Millar and Gregory (*43*), in a study of both fresh heparinized blood and ACD-stored blood from a blood bank, showed a reduction in the oxygen carrying capacity of up to 10 percent in the blood of cigarette smokers; this reduction persisted for the full 21-day storage life of blood bank blood.

Cole, et al. (*16*), in a study of pregnant women, found COHb levels in the fetus to be 1.8 times as great as those in the

simultaneously measured blood of the mother. Fetal blood was exposed to carbon monoxide in vitro, and fetal hemoglobin was found to have a shift of the oxyhemoglobin disassociation curve to the left as occurs with adult hemoglobin. The higher fetal COHb levels were attributed to the lower fetal Po_2 and a resultant decrease in the ability of oxygen to compete for the fetal hemoglobin. It was felt by the authors that the high COHb levels may be responsible for the lower birth weight of infants born to mothers who smoke.

Effects on Persons with Atherosclerotic Cardiovascular Disease

Aronow and Isbell (*5*) and Anderson, et al. (*1*) have shown a decrease in the mean duration of exercise before the onset of pain in patients with angina pectoris exposed to low levels of carbon monoxide (50 and 100 ppm). Carboxyhemoglobin levels were significantly elevated (2.9 percent after 50 ppm; 4.5 percent after 100 ppm) and the systolic blood pressure, heart rate, and product of systolic blood pressure times heart rate (a measure of cardiac work) were all significantly lower at onset of angina pectoris.

In a continuation of this work, Aronow, et al. (*2, 3*) studied eight patients during two separate cardiac catheterizations, one during which each patient smoked three cigarettes and one during which each patient inhaled carbon monoxide until the maximal coronary sinus COHb level equalled that produced by smoking during the first catheterization. All eight had angiographically demonstrated CHD (> 75 percent obstruction of at least one coronary artery). Smoking increased the systolic and diastolic blood pressure, heart rate, left ventricular end-diastolic pressure (LVEDP), and coronary sinus, arterial, and venous CO levels. No changes were noted in left ventricular contractility (dp/dt), aortic systolic ejection period, or cardiac index, and decreases were found in stroke index and coronary sinus, arterial, and venous Po_2. When carbon monoxide was inhaled, increased LVEDP and coronary sinus, arterial, and venous CO levels were noted; there were no changes in systolic and diastolic blood pressure, heart rate, or systolic ejection period; and decreases in left ventricular dp/dt, stroke index, cardiac index and coronary sinus, arterial, and venous Po_2 were found. These data suggest that carbon monoxide has a negative inotropic effect on myocardial tissue resulting in the decrease in contractility (dp/dt) and stroke index. When the positive effect of nicotine on contractility and heart rate is added by cigarette smoking, the net effect is increased cardiac work for the same cardiac output. In the heart with

coronary artery disease there is a greatly restricted capacity to increase blood flow in response to this increase in cardiac work. The result is early cardiac decompensation manifested by elevation in LVEDP and angina pectoris.

Aronow, et al. have also shown decreased exercise time prior to onset of angina pectoris in persons exercised after riding for 90 minutes on the Los Angeles Freeway (*4*). In a related study, they demonstrated a decrease in exercise time before claudication in a group of patients with intermittent claudication who were exposed to 50 ppm CO (*6*).

Studies on the Pathogenesis of Cardiovascular Disease

In a review of some of their work on carbon monoxide, Astrup and Kjeldsen (*7*) noted that in cholesterol-fed rabbits exposed to 170 ppm carbon monoxide for 7 weeks (COHb 16 percent) and then to 340 ppm for 2 weeks, the cholesterol content of the aorta was 2.5 times higher than that of cholesterol-fed, air breathing controls. Groups of cholesterol-fed rabbits intermittently exposed to carbon monoxide for 12 or 4 hours per day produced three- to fivefold increases in the cholesterol content of their aortas. Cholesterol-fed rabbits made hypoxic at 10 and 16 percent oxygen had 3 to 3.5 times the aortic cholesterol content, while those exposed to 26 and 28 percent oxygen had a considerable decrease in cholesterol accumulation.

Theodore, et al. (*58*) studied the aortas of monkeys, baboons, dogs, rats, and mice fed a normal diet but exposed to very high levels of CO (COHb levels 33 percent) and found no atheromatous changes in their aortas.

Further work by Astrup and Kieldsen (*38*) revealed that in rabbits fed normal diets but exposed to 180 ppm carbon monoxide for 2 weeks, there were local areas in their hearts of partial or total necrosis of myofibrils; in the arteries there was endothelial swelling, formation of subendothelial edema, and degeneration of the myocytes. When the aortas of these rabbits were examined (*37*), the luminal coats showed pronounced changes characterized by severe edematous reaction with extensive swelling and formation of subendothelial blisters and plaques. The authors postulate that carbon monoxide increases endothelial permeability to albumin which results in formation of edema leading to changes indistinguishable from early atherosclerosis.

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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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.

the nonsmoking controls. No relationship of this increased prevalence could be demonstrated to alpha$_1$-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$_1$-antitrypsin (A_1AT)—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$_1$-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_1AT 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-

ciated with a particular type of pulmonary emphysema. While the majority of lungs of emphysematous patients reveal bullous or centrilobular deformities, particularly of the upper lobes, this hereditary disorder reveals a panacinar change, most severe in the lower lobes (*101, 215, 226*). Patients with emphysema who are found to have the homozygous deficiency have been observed to include a greater percentage of female patients than is usually observed in the general emphysema population. Their disease begins earlier, is more severe, is characterized by dyspnea rather than cough, and frequently is unassociated with a history of preceding bronchitis (*101, 215, 226*). Radiographic studies of A_1AT-deficient patients have revealed decreased vascularization of the lower lobes and increased vascularization of the upper lobes (*101, 213*). It is estimated that between 1 and 2 percent of patients with COPD have this homozygous deficiency (*78, 216*). In family studies, it has been found that almost all the homozygous individuals are symptomatic by the age of 40 and that those who are not usually show alterations in pulmonary function studies. Guenter, et al. (*98*) studied 7 persons with homozygous deficiency. Of the five symptomatic individuals, 4 smoked and all had abnormal timed vital capacity. Neither of the two asymptomatic individuals smoked or had this change in vital capacity. All 7, however, were noted to be hypoxemic at rest and to have decreased pulmonary diffusing capacity.

It has been suggested (*154*) that the lack of this proteinase inhibitor in the serum of homozygous patients predisposes them to emphysema in the following manner: Leukocytes present in the blood contain significant amounts of proteinase enzymes as part of the overall defense mechanism against infection; the breakdown of these cells during acute infection releases proteinases into the pulmonary tissues and these, without the presence of a normal inhibitor, may contribute to the breakdown of the structural proteins of lung tissue.

Heterozygous individuals have been defined as those who show levels of A_1AT intermediate between those of normals and those with homozygous deficiency. At the present time, there is much debate about whether or not heterozygotes for A_1AT are at a greater risk of developing COPD than are A_1AT normals. A major difficulty is the lack of a precise definition of heterozygosity. At present, the best method for the determination of the level of A_1AT appears to be that of crossed serum immunoelectrophoresis because levels of trypsin inhibitory capacity (TIC) have been shown to rise acutely with infections.

Welch, et al. (*226*) feel that heterozygotes do not show an increased susceptibility to COPD. The heterozygotes which they studied showed symptoms of bronchitis and did not present the

lower lobe perfusion defects frequently noted in homozygotes. They also found no difference in the number of COPD patients among the heterozygotic and the general population. Other investigators, notably Lieberman, et al. (*154, 155*), Kueppers, et al. (*144*), and Larson, et al. (*148*) found significantly increased percentages of COPD patients among those with heterozygous deficiency as compared with the general population. Lieberman, et al. (*155*) observed that the percentage of heterozygotes among a group of healthy industrial workers was 4.7 percent while that among a group of patients with emphysema was 18.1 percent. In a recent review, Falk and Briscoe (*79*) considered that the available evidence points to an increased prevalence of COPD among heterozygotes.

Of more central interest to this discussion, however, is the possible relationship of smoking to the predisposition of disease among the heterozygote population. Kueppers, et al. (*144*) studied three populations: younger controls, older controls, and a group of COPD patients. They observed that of the 25 heterozygotes with COPD, only 2 were over 70 years of age, both were female and nonsmokers. The remaining 23 were cigarette smokers. Nevertheless, studies which adequately sort out the factors of genetic susceptibility and cigarette smoke exposure have yet to be reported.

An important question is to what extent the relationship between smoking and COPD is influenced by identifiable genetic factors. At present, it is possible to identify what appears to be only a very small group of susceptibles for whom genetic factors may be paramount in the pathogenesis of their ailment. Of greater public health import is whether lesser degrees of genetically identifiable susceptibility interact with cigarette smoking to account for a significant proportion of the problem.

Air Pollution

Numerous epidemiological studies have been conducted in order to examine the effect of air pollution on human nonneoplastic respiratory disease. Three major types of studies have been utilized: observation of the mortality and morbidity due to an acute episode of increased air pollution, observation of the day-to-day variation in mortality and its relation to air pollution levels, and geographical comparisons. The majority of studies fall into the third category, and these are detailed in table A6.

A number of studies did not show an association among air pollution, respiratory symptoms, and pulmonary dysfunction (*81, 204*). More recent studies which evaluated the factors of smoking, social class, and air pollution separately noted a greater prevalence of

COPD symptoms, pulmonary dysfunction, and COPD mortality in areas of high pollution (*12, 122, 146, 233*). Lambert and Reid (*146*) observed that in the absence of cigarette smoking the correlation between COPD symptoms and air pollution was slight and suggested that the two factors may interact to produce higher rates of disease.

The evidence which has accumulated in the past 7 years gives further support to the conclusion of the Surgeon General's Advisory Committee on Smoking and Health as stated in its 1964 Report that: "For the bulk of the population of the United States, the relative importance of cigarette smoking as a cause of chronic bronchopulmonary disease is much greater than atmospheric pollution or occupational exposures."

Occupational Hazards

Exposure to various dusty occupational environments has been shown in many studies to be associated with the development of various forms of nonneoplastic lung disease. Lowe (*158*), in a review of the relationship of occupational exposure and chronic bronchitis, noted that among workers exposed to dust significant increases in COPD mortality were observed. These occupations included coal mining, tinning, galvanizing, riveting, and caulking. Commenting on a previously unreported study of more than 20,000 steel workers, he observed that the relationship between mean dust exposure levels and COPD prevalence was much stronger among smokers than among nonsmokers.

More recently, Bouhuys and Peters (*37*) reviewed those specific industrial exposures related to lung disease. COPD was found to be associated with exposure to coal dust, asbestos, bagasse dust, isocyanates, various irritant gases, and textile dusts (cotton, flax, or hemp).

Studies which have investigated the interrelationship between smoking, industrial exposure, and COPD are listed in table A7. Additional compounds, not listed in the table, but which also appear to be related to COPD, are chlorine (*49*) and washing powder dust (*97*). Cigarette smoking and harmful dust exposures appear to act in a combined manner in the production of COPD.

Although an increased prevalence of COPD is found with certain occupational exposures, in none is the relationship as strong as that between COPD and cigarette smoking. To demonstrate an increased occupational risk, careful analysis of smoking habits is required. The relative importance of cigarette smoking appears to be much greater than occupational exposure as an etiologic factor in COPD.

Cadmium—Chronic industrial exposure to cadmium in man has been found to induce pulmonary emphysema without significant accompanying chronic bronchitis (*34, 35, 210*).

Nandi, et al. (*177*) recently investigated the contribution of the cadmium in cigarette smoke to the pathogenesis of emphysema. Analyzing whole cigarettes, ash, and filters, they found that an average of 69 percent of the cadmium present in the cigarette (approximately 16 micrograms 20 cigarettes) is inhaled in the smoke. In a related study (*153*), these investigators showed that the level of cadmium in water-soluble liver protein on autopsy was three times greater in those patients with a history of chronic bronchitis/emphysema than that found in those without such a history. Unfortunately, no smoking histories were available.

PATHOLOGICAL STUDIES

The relationship between smoking habits and pathological changes in the bronchial tree and pulmonary parenchyma has been investigated by several groups of workers. Metaplastic changes, although found in nonsmokers, are much more common in smokers (table 10, Cancer Chapter), and a dose-relationship of increasing metaplasia with increased smoking has been evident in many of the studies.

Pathological studies which deal primarily with pulmonary parenchymal and non-metaplastic bronchial changes are presented in table 8. Goblet cell distention, alveolar septal rupture, thickened bronchial epithelium, and mucous gland hypertrophy have been found to be more frequent in smokers than in nonsmokers. Auerbach, et al. (*17*) noted a dose-response relationship between the amount of smoking and the degree of septal rupture.

Anderson, et al. (*4, 5*) studied the difference in the type of emphysema shown by smokers and nonsmokers. In their study, listed in table 8, they noted that the group of patients with panlobular emphysema was comprised of equal numbers of smokers and nonsmokers while of patients with centrilobular emphysema, 98 percent were smokers. More recently, the same authors studied lung macrosections from 80 nonsmokers. While most were normal, 24 demonstrated parenchymal dilatation and disruption consistent with panlobular emphysema. Thurlbeck, et al. (*217*) have also observed that centrilobular emphysema rarely occurs in nonsmokers.

TABLE 8.—*Studies concerning the relation of human pulmonary histology and smoking*[1]

(Actual number of deaths shown in parentheses)

SM = Smokers. NS = Nonsmokers

Author, year, country, reference	Number and type of population	Results	Comments
Chang, 1957, U.S.A., Korea (47).	62 males and 43 females autopsied within 5 hours of death (no data available on case selection).	*Distention of goblet cells (by percent of smoking group)* *None* / *Few* / *⅓ of surface* / *½ of surface* / *Most of surface* / *Whole surface* NS(22) . 13.6 / 22.7 / 31.8 / 22.7 / 9.1 / .. SM(49) . 12.2 / 10.2 / 10.2 / 18.4 / 26.5 / 22.5	The authors also noted that smokers' lungs showed shorter cilia and thicker epithelium (20 percent nonsmokers and 36 percent smokers had respiratory disease.)
Ide et al., 1959, U.S.A. (*123*).	93 males autopsied within 6 hours of death. No cases of pneumonia or lung disease included.	*Mean thickness of tracheal and bronchial epithelium (μ) in cigarette smokers and nonsmokers* / *Mean ciliary height in trachea and bronchus on cigarette smokers and nonsmokers* *Trachea* / *Bronchus* / *Trachea* / *Bronchus* NS(23) ..... 52.8 / 47.7 / (23) 6.39 / 5.95 Light(31) ..... 62.0 / 57.5 / (29) 5.62 / 5.40 Heavy(10) ..... 66.2 / 61.9 / (10) 4.89 / 4.66	No cigar or pipe smokers were included.
Auerbach et al., 1963, U.S.A. (*17*).	654 males over 60 years of age autopsied at East Orange VA Hospital.	*Age-standardized percentage distribution of subjects according to degree of rupture of the alveolar septums* *Degree of rupture* / *0–0.25* / *0.5–0.75* / *1.0–1.25* / *1.5–1.75* / *2.0–2.25* / *2.5–3.00* Never smoked ..... 19.4 / 50.5 / 24.0 / 3.6 / 1.6 / .. Current cigarette .... / .4 / 5.1 / 16.2 / 39.2 / 39.1 †Current cigar .... / 24.6 / 45.4 / 26.2 / 3.8 / .. †Current pipe ..... 5.4 / 23.0 / 53.5 / 15.9 / 2.2 / .. Current pipe, cigar ..... 4.8 / 7.6 / 46.5 / 33.6 / 7.5 / ..	The authors also noted a dose-response relationship between smoking and degree of rupture. †None had ever smoked cigarettes regularly.

TABLE 8.—*Studies concerning the relation of human pulmonary histology and smoking* (cont.)

(Actual number of deaths shown in parentheses)

SM = Smokers. NS = Nonsmokers

Author, year, country, reference	Number and type of population	Results	Comments
Anderson et al., 1964, U.S.A. (5).	39 males and 32 females (Caucasians) undergoing routine autopsy (40-97 years of age.)	*Severity of emphysema (mean degree)* *Males*: NS(4) 1.5; SM(35) 2.8 (not significant) *Females*: (20) 1.0; (12) 1.9 ($p<0.05$)	The authors also noted that: Every person showing severe disease was a smoker. Among those with panlobular emphysema, there was an equal distribution of smokers and nonsmokers while among those with centrilobular emphysema 98 percent were smokers and only 2 percent were nonsmokers.
Anderson et al., 1966, U.S.A. (6).	107 males and 58 females autopsied for whom smoking data was available.	*Percentage distribution of tobacco users in 165 necropsies by degree of emphysema severity* None 36 (12/33) Mild 69 (58/84) Moderate 91 (30/33) Severe 93 (14/15) *Mean severity of emphysema* SM(114) 2.3; NS(51) 0.9 ($p<0.001$) Male(107) 2.2; Female(58) 1.2 ($p<0.001$) Never smoked 0.9 <20 cigarettes/day 1.9 20-40 cigarettes/day 2.4 >40 cigarettes/day 2.3	
Megahed et al., 1967, Egypt (165).	50 male patients with chronic bronchitis undergoing bronchial biopsy and lavage.	*Mucous gland hypertrophy* *Percent* NS 29 (2/7) SM 77 (33/43) ($p<0.02$)	

TABLE 8.—*Studies concerning the relation of human pulmonary histology and smoking* (cont.)

(Actual number of deaths shown in parentheses)

SM = Smokers. NS = Nonsmokers

Author, year, country, reference	Number and type of population	Results						Comments
			Degree of tracheal and bronchial arteriolar thickening (by percentage of smokers)					
			0.0–0.4	*0.5–0.9*	*1.0–1.4*	*1.5–1.9*	*2.0+*	
Auerbach et al., 1968, U.S.A. (*14*).	562 males autopsied at East Orange VA Hospital.	Never smoked (122)	46.1	39.3	13.3	1.3	..	
		<20 cigarettes/day (120)	11.7	22.0	33.6	28.4	4.4	
		20–40 cigarettes/day (254)	5.0	8.6	37.4	40.9	8.1	
		>40 cigarettes/day (66)	1.3	1.4	31.5	45.3	20.5	

[1] Numerous experiments detailing changes in bronchial epithelium are detailed tabularly in the Cancer chapter.

EXPERIMENTAL STUDIES

ANIMAL STUDIES

A number of investigators have studied the effect of the inhalation of cigarette smoke on the macroscopic and microscopic structure of the tracheobronchial tree and pulmonary parenchyma of animals. Studies dealing with metaplasia and cellular atypism of the trachea and bronchi are listed in table A16 of the cancer chapter. Studies more directly concerned with the pathology of COPD are listed in table 9. They show that cigarette smoke exposure is associated with changes similar to those found in humans with COPD, i.e., bronchitis, parenchymal disruption, alveolar septal rupture, alveolar space dilatation, and the loss of cilia and ciliated cells in the bronchial mucosa.

The investigations of Auerbach and his coworkers (*15, 16, 88*) have demonstrated by the use of both light and electron microscopy that dogs who inhale cigarette smoke through tracheostomas develop progressively more severe lesions of the bronchi and parenchyma with increased exposure to cigarette smoke. In electron microscopic studies of specimens taken from the lungs of dogs thus exposed to cigarette smoke, the following changes were observed: In 5 dogs sacrificed after only 44 days of smoking exposure, there was a proliferation of goblet cells as well as a partial loss of cilia in the lining cells, and in 5 dogs sacrificed after 420 days or more of exposure, the number of cell layers in the bronchial epithelium was found to be twice that of the nonsmoking dogs. Goblet cells and ciliated columnar cells were no longer present; instead, the surface was lined with columnar and cuboidal cells with stubby projections in place of cilia. Mitotic figures were frequently observed in the basal cells. These findings may be relevant to carcinogenesis as well as to the development of COPD.

In a long-term experiment, carried out by the same group, dogs were exposed to varying doses of cigarette smoke. Details of the experimental procedure have been outlined in the section on Pulmonary Carcinogenesis. The animals were separated into nonsmoker, filter-tip cigarette, nonfilter-light, and nonfilter-heavy exposure groups. The dogs were "smoked" for 875 days, or approximately 29 months. The animals which died during the experiment and the animals sacrificed after day 875 were examined for pulmonary parenchymal changes as well as for bronchial epithelial alterations. As seen in figures 1 and 2, dose-related pathological changes, including fibrosis and emphysema, were found in the lung parenchyma of the exposed dogs. These changes were similar to those seen in the lungs of humans with COPD.

TABLE 9.—*Experiments concerning the effect of the inhalation of cigarette smoke upon the tracheo-bronchial tree and pulmonary parenchyma of animals*[1]

(Actual number of animals shown in parentheses)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results
Leuchtenberger, et al., 1960, U.S.A. (*152*).	603 CF_1 female mice.	A. Inhalation. B. Up to 8 cigarettes/day for up to 2 years. C. Cigarette smoke.	*Number of mice showing specified changes* *Months exposure* / *Number of cigarettes* / *Number of mice* / *No change* / *Mild bronchitis* / *Severe bronchitis with atypism* 0 / 0 / 150 / 146 / 2 / 2 (no atypism) 1–3 / 100–200 / 36 / 20 / 9 / 7 4–8 / 250–500 / 36 / 19 / 10 / 7 9–23 / 600–1600 / 34 / 19 / 7 / 8 1–23 / 25–1526 / 151 / 88 / 33 / 30
Holland et al., 1963. (*123*).	60 rabbits.	A. Inhalation. B. Up to 20 cigarettes/day for 2–5. C. "Normal cigarette smoke".	*Cytology of tracheobronchial mucosa* *Normal* / *Focal hyperplasia* / *Generalized hyperplasia* / *Generalized emphysema* Controls ..... (30) 21/30 / 6/30 / 3/30 / 1/30 Exposed ..... (30) 7/30 / 10/30 / 9/30 / 11/30
Hernandez et al., 1966 U.S.A. (*111*).	Adult Greyhound dogs.	A. Inhalation. B. Twice daily/5 per week. C. Cigarette smoke.	*Number of sections* / *Mean number of months* / *Mean parenchymal disruption/dog* / *Groups compared* / *P-value* I. Controls ..... (8) 112 / .. / 0.7150 / I–III / insignificant II. All exposed ..... (15) 205 / 10.50 / 0.9383 / II–I / insignificant III. Exposed <1 year ..... (7) 98 / 4.60 / 0.6421 / III–IV / $p < 0.05$ IV. Exposed >1 year ..... (8) 107 / 14.74 / 1.2350 / IV–I / $p < 0.02$

TABLE 9.—*Experiments concerning the effect of the inhalation of cigarette smoke upon the tracheo-bronchial tree and pulmonary parenchyma of animals*[1] *(cont.)*

(Actual number of animals shown in parentheses)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results
Auerbach et al., 1967, U.S.A. (*15, 16*).	Beagle dogs.	A. Active inhalation via tracheostomy. B. Up to 12 cigarettes per day for up to 423 days. C. Cigarette smoke.	Controls ....(10)—No evidence of pulmonary fibrosis or septal rupture. Exposed ....(10)—*Early (sacrificed)*: 1. Alveolar space dilatation. 2. Pad-like attachments to alveolar septa. *Medium exposure*: Septal wall thickening. *Latest exposure*: 1. Focal subpleural pulmonary fibrosis. 2. Ruptured alveolar septa. 3. Granulomata.
Frasca et al., 1968, U.S.A. (*88*).	Beagle dogs.	A. Active inhalation via tracheostomy. B. Up to 12 cigarettes per day for up to 423 days. C. Cigarette smoke.	Electron microscopic results: After 44 days — Increased number of goblet cells. Decreased number of cilia on surface lining cells. After 420 days— Increased number of epithelial cell layers. Loss of ciliated columnar cells. Frequent interruptions in basement membrane.

[1] Numerous experiments detailing changes in bronchial epithelium are detailed tabularly in the Cancer Chapter.

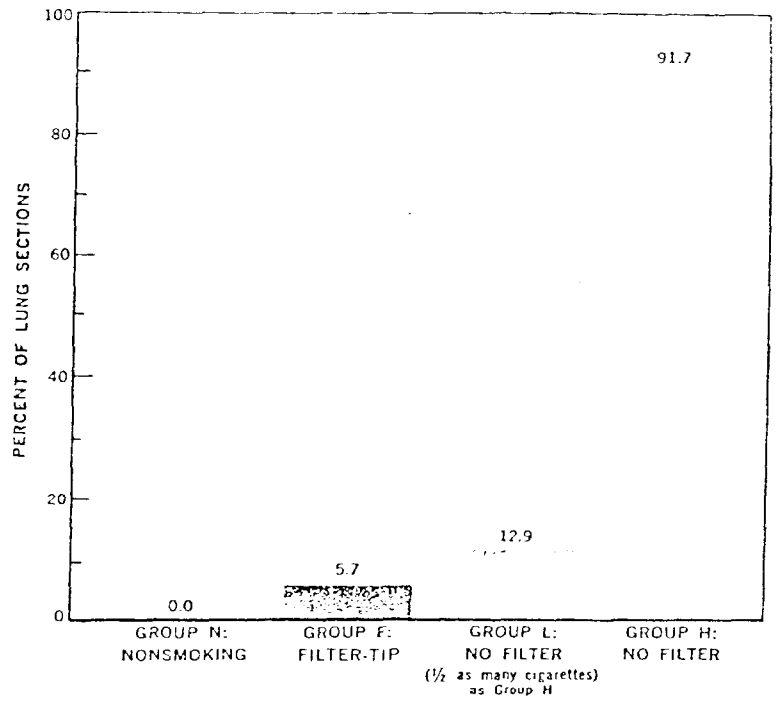

FIGURE 1.—Percent of lung sections with grade IV or V fibrosis.
SOURCES: Hammond, et al. (*104*).

Several investigative groups have exposed rodents to various ambient concentrations of nitrogen dioxide over prolonged periods of time. This gas is found in cigarette smoke and in some industrially polluted air. The results of these studies are outlined in table A10. It is clear that chronic exposure to low levels of NO_2 is capable of inducing lesions in the bronchial tree although the relationship between these changes, cigarette smoking, and the development of COPD remains to be determined.

Rosenkrantz, et al. (*196, 197*) have recently undertaken experiments dealing with pulmonary cellular metabolism. They exposed Swiss albino mice to cigarette smoke or its vapor phase for varying lengths of time. On autopsy, animals exposed to cigarette smoke showed elevations in the levels of lung DNA, lactate, and glycogen which the authors conclude reflect hyperplasia and macrophage infiltration. Similarly, a dose-related increase in lung hydroxyproline was observed. This was considered to be due to increased fibroblastic collagen synthesis.

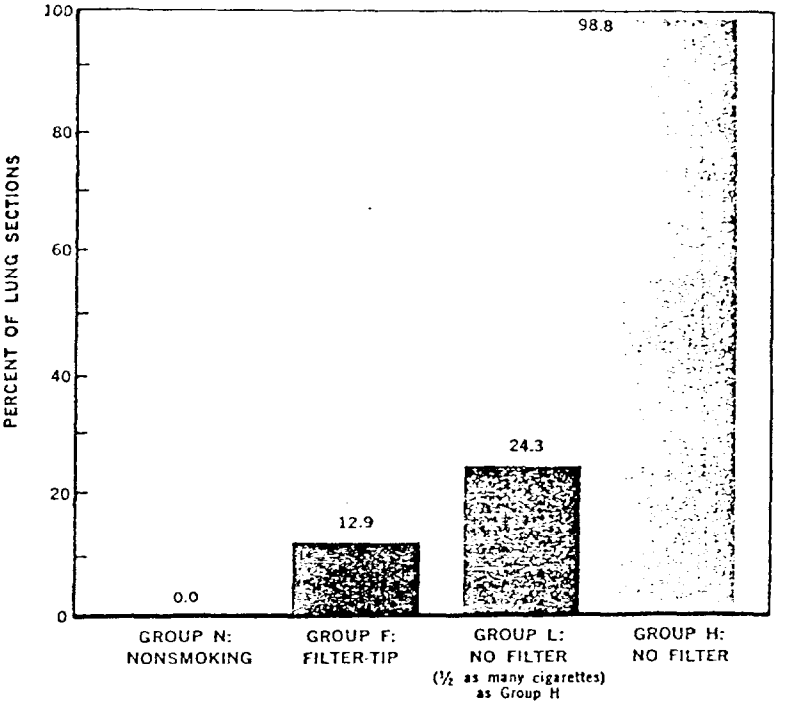

FIGURE 2.—Percent of lung sections with grade II or III emphysema.
SOURCES Hammond, et al. (*104*).

Aviado and coworkers have performed a series of experiments on live animals and in heart-lung preparations to study the effect of cigarette smoke on pulmonary physiology and structure (*18, 19, 20, 21, 22, 179, 180, 199, 200, 201, 202*). The authors observed that cigarette smoke causes acute bronchoconstriction both by the release of histamine and the stimulation of parasympathetic nerve pathways in the lung. Bronchial arterial injections of nicotine were found to cause reactions similar to those observed after cigarette smoke inhalation. The bronchoconstriction was usually followed by bronchodilatation which the authors attributed to sympathetic stimulation. As mentioned in the Chapter on Cardiovascular Diseases, nicotine has been shown to induce the release of catecholamines.

Experiments by Aviado and coworkers as well as other authors (*66, 99*) using guinea pigs showed that exposure to cigarette smoke was associated with increased bronchopulmonary resistance and decreased pulmonary compliance. The authors related these changes to the bronchoconstriction of terminal ventilatory units.

Similar experiments in dogs showed that the increase in resistance following either cigarette smoke exposure or intravenous nicotine could be blocked by pretreatment with atropine. As a parasympathetic blocker, atropine would decrease the acute bronchoconstrictive phase.

Most recently, Aviado and his colleagues (*20, 130*) have attempted to induce physiologic and anatomic changes similar to those found in the lungs of patients with emphysema. They exposed male rats to cigarette smoke, the introduction of the enzyme papain, as well as to partial tracheal ligation. In 10 rats exposed to cigarette smoke twice daily for 30 minutes over a period of 10 weeks, no changes in pulmonary compliance or resistance were noted. Also, no abnormal histological changes were observed in the group exposed only to cigarette smoke. However, animals who underwent tracheal ligation as well as smoke exposure showed increased numbers of enlarged air spaces and increased pulmonary resistance when compared with animals who underwent only tracheal ligation.

Studies in Humans

The acute effects of cigarette smoke inhalation on bronchopulmonary function in man have been investigated by a number of workers. The results of these studies are presented in table 11. The majority of studies, particularly the more recent ones, found that the inhalation of cigarette smoke is associated with an acute increase in pulmonary resistance and a decrease in pulmonary compliance. Chapman (*48*) also observed decreases in pulmonary diffusing capacity and arterial O_2 tension. Chiang and Wang (*51*) noted changes in nitrogen washout time and alveolar dilution factor, alterations which reflect impaired alveolar ventilation and gas mixing.

James (*131*) examined the effect of prior smoking on the multiple breath nitrogen washout test in 41 pneumoconiotic miners and 5 normal young males. Prior smoking of a cigarette in the subject's normal manner was found to adversely affect the indices of distribution in 20 percent of the miners and in all of the 5 normals who smoked within one hour of testing. The author suggests that smoking be prohibited prior to any series of pulmonary function studies.

Anderson and Williams (*9*) studied the acute effect of cigarette smoke inhalation upon the ventilation-perfusion (V/Q) measurements in the lung in normals and in patients with COPD. Cigarette smoking was observed to cause acute changes in the V/Q measurements, and the COPD patients were found to be particularly liable to these changes.

Finally, Robertson, et al. (*194*) studied the effect of unfiltered and filtered cigarette smoke and cigar smoke upon bronchial reactivity in 19 of the most reactive persons in a group of 91 heavy smokers. They observed that bronchial reactivity was significantly reduced by increasing the retention efficiency of the filter and that reactivity to inhaled cigar tobacco was no less than that to cigarette smoke. They concluded that differences in inhalation account for the difference in COPD prevalence observed between cigarette and cigar smokers.

Studies Concerning Pulmonary Clearance

Overall Clearance

The ability of the lung to rid itself of inhaled particles that cannot be easily exhaled is dependent upon a number of physiologic mechanisms including ciliary activity, the mucous sheath, and the pulmonary alveolar macrophage. Studies concerning the effect of human cigarette smoking and the exposure of animals to cigarette smoke on this clearance system are presented in table A13. LaBelle, et al. (*145*) and Bair and Dilley (*23*) observed no change in clearance following the exposure of rats, rabbits, or dogs to cigarette smoke. The latter authors noted, however, that normal clearance rates obtained prior to smoking were too low to reflect any significant change except complete cessation.

Albert, et al. (*3*) exposed donkeys to cigarette smoke via nasal catheter and observed impairment of clearance times. Holma (*125*) obtained similar results in rabbits.

In a related study, Albert, et al. (*2*) studied the bronchial clearance times of 9 nonsmokers and 14 cigarette smokers in a total population of 36 subjects. The rates of bronchial clearance were slower on the average in the cigarette smokers when compared with the nonsmokers, although a wide variation was present in each group. In relation to their study mentioned above, they also noted that the shape of the whole lung clearance curves seen in smokers (with markedly prolonged 50 percent clearance times) was similar to that developed in the donkey following acute exposures to sulfur dioxide or cigarette smoke.

Ciliary Function

Numerous experiments have shown that cigarette smoke or certain constituents of cigarette smoke adversely affect and can even bring about a cessation of ciliary activity in respiratory epithelium *in vivo* and *in vitro* in cultures of ciliated microorganisms. The results of a number of these experiments are presented in table 12.

Ciliary activity has been shown to be affected by particulate matter as well as by the gas phase components of cigarette smoke. The relative importance of these two large classes of components of smoke in producing ciliastasis is presently a matter of some discussion. Dalhamn and Rylander (*63*, *64*) consider the particulate phase to be of greater importance while Battista and Kensler (*28*, *29*) conclude that gas phase components are more important in the induction of ciliastasis.

Studies investigating the effect of cigarette smoke on the morphology of the tracheobronchial tree in animals have noted a decrease or absence in the number of cilia in smoke-exposed animals. Recently, Kennedy and Elliot (*134*) studied the effect of the direct exposure of cigarette smoke upon the electron microscopic structure of protozoan mitochondria. After 42 minutes of exposure to mainstream smoke, they noted destruction of the internal membrane structure of the mitochondria.

Thus, cigarette smoke has been shown to be toxic to ciliary function by pathological (including electron microscopic) and physiological methods.

Phagocytosis

The effect of cigarette smoke upon pulmonary alveolar phagocytosis, one part of the clearance mechanism, has been studied by several authors. Masin and Masin (*162*) observed increased variation in the size of lipid inclusions in sputum macrophages obtained from smokers as compared to those obtained from nonsmokers. They attributed these differences to a combined effect of irritation of the alveolar lining, increased turnover of alveolar cells, and increased injury to the macrophages. Green and Carolin (*96*) noted that cigarette smoke inhibited the ability of rabbit alveolar macrophages to clear cultures of *S. aureus*. This effect was noticeably reduced by filtration. Similarly, Yeager (*239*) exposed rabbit alveolar macrophages which had been induced by *M. bovis* to cigarette smoke and observed a dose-dependent decrease in protein synthesis. This alteration occurred at smoke solution concentrations that did not affect cell viability. The alteration was only partly reversible and was due mainly to gas phase components. Myrvik and Evans (*175*) observed similar protein synthesis alterations in macrophages exposed to NO_2.

Roque and Pickren (*195*) obtained alveolar macrophages at thoracotomy from 17 smokers and 4 nonsmokers. They found a decrease in the activity of oxidoreductases and hydrolases in the macrophages of smokers. The reduction in the enzymatic activity was directly proportional to the amount of stored fluorescent material present in the macrophages. This material was thought to

TABLE 11.—*Experiments concerning the acute effect of cigarette smoke inhalation on human pulmonary function*

Author, year, country, reference	Number and type of population	A. Method [1] B. Material [1] C. Duration of smoking	Results		Comments
Bickerman and Barach, 1954, U.S.A. (*31*).	I. 66 male and 25 female patients with chronic nontuberculous respiratory diseases (average age 50). II. 20 male and 7 female normal subjects (average age 20).	A. Pulmonary function. B. 3 cigarettes. C. 30 minutes.	*Vital capacity (VC)* I. 10/91 decrease. II. No significant change.	*Maximal breathing capacity* 10/91 decrease. No significant change.	9/91 patients showed VC increase due to clearance of secretions. All mild or moderate smokers.
Elch, et al., 1957, U.S.A. (*76*).	I. 31 patients with obstructive pulmonary emphysema. II. 14 normal subjects. III. 5 patients with respiratory complaints. All habitual smokers.	A. Esophageal balloon technique to measure pulmonary compliance and resistance. B. 1 cigarette. C. Undefined.	*Mean airway resistance* I. Statistically significant increase. II. No change. III. No change.	*Mean airway compliance* No change. No change. No change.	

TABLE 11.—*Experiments concerning the acute effect of cigarette smoke inhalation on human pulmonary function (cont.)*

Author, year, country, reference	Number and type of population	A. Method [1] B. Material [1] C. Duration of smoking	Results		Comments
Attinger et al., 1958, U.S.A. (*15*).	I. 20 normal subjects (10 Sm, 10 NS). II. 34 patients with various diseases; 9 rheumatic heart diseases, 8 pulmonary emphysema, 7 asthma, 5 pulmonary fibrosis, 5 undefined.	A. Esophagal balloon technique to measure pulmonary compliance and resistance. B. 1–4 cigarettes. C. 10 minute interval between cigarettes.	I. No change. II. Expiratory resistance rose significantly only among patients with emphysema.	No change. No change.	
Motley and Kuzman, 1958, U.S.A. (*174*).	125 males and 16 females (24–70 years of age—normals and patients).	A. Pulmonary function. B. 2 cigarettes. C. Undefined.	41 smokers (8 normals, 33 patients with cardiopulmonary disease).	*Pulmonary compliance* Significant decrease after smoking.	Various groups of normals and cardiopulmonary patients showed little or no change in arterial pO_2 during exercise and at rest following cigarette smoke inhalation.
Nadel and Comroe, 1961, U.S.A. (*176*).	I. 22 patients with cardiopulmonary disease—all smokers. II. 36 normals (21 smokers, 15 nonsmokers).	A. Body plethysmography. B. 15 puffs. C. 5 minutes.	*Airway conductance/thoracic gas volume* I. 18/22 significant decrease (inhibited by pretreatment with isoproterenol aerosol). II. 31/36 significant decrease (inhibited by pretreatment with isoproterenol aerosol).		Nicotine bitartrate aerosol evoked no change.

TABLE 11.—*Experiments concerning the acute effect of cigarette smoke inhalation on human pulmonary function (cont.)*

Author, year, country, reference	Number and type of population	A. Method [1] B. Material [1] C. Duration of smoking	Results		Comments
Simonsson, 1962, Sweden, (207).	I. 9 male and 7 female normals (*most smokers*). II. 15 male and 1 female pulmonary disease patients (*most smokers*).	A. *Pulmonary* function. B. 1-2 cigarettes. C. 5-6 minutes per cigarette.	*Mean* $FEV_{1.0}$ (*immediately after*) I. Significant decrease. II. Significant decrease.	*Mean* $FEV_{1.0}$ (*45 minutes later*) No significant decrease. Significant decrease.	No significant changes observed in FEV/FVC.
Zamel et al., 1963, England, (240).	I. 6 male and 6 female nonsmokers. II. 6 male and 6 female smokers (18–32 years of age.)	A. Body plethysmography. B. 1 cigarette. C. Undefined.	*Airway resistance* I. Significant increase. II. Significant increase.		
Chapman, 1965, Ireland (48).	I. 12 normal volunteers (all smokers). II. 6 patients with chronic non-specific lung disease.	A. Pulmonary function Arterial blood studies. B. 1 cigarette. C. Undefined.	I. All showed a decrease in diffusing capacity. II. 4/6—significant decrease in arterial 0_2 tension. No change in vital capacity or FEV.		
McDermott and Collins, 1965, Wales (160).	I. 32 normals. II. 28 with chronic bronchitis (All cigarette smokers 35–60 years of age.)	A. Body plethysmography. B. Cigarette. C. Undefined.	*Mean airway resistance* I. Significant increase. II. Significant increase.		Light smokers showed greater changes than heavy smokers.

TABLE 11.—*Experiments concerning the acute effect of cigarette smoke inhalation on human pulmonary function (cont.)*

Author, year, country, reference	Number and type of population	A. Method [1] B. Material [1] C. Duration of smoking	Results			Comments
Miller and Sproule, 1966, U.S.A. (*166*).	10 normal cigarette smokers (40 years of age).	A. Esophageal balloon technique. B. 1 cigarette. C. One inhalation every 30–60 seconds.	$FEV_{0.5}$ No significant change	*Dynamic compliance* Significant decrease.	*Inspiratory and expiratory resistance* Significant increase	
Sterling, 1967, England (*213*).	11 normal adults (8 smokers, 3 nonsmokers).	A. Body plethysmography. B. 15 inhalations. C. 5 minutes.	*Airway resistance* Significant increase (Return to normal in 30 minutes).			
Chiang and Wang, 1970, Formosa (*51*).	7 male normal nonsmokers (18–43 years of age).	A. Pulmonary function Nitrogen washout. B. 2 cigarettes. C. Undefined.	*Nitrogen washout time* Significant increase.	*Lung clearance index* Significant increase.	*Alveolar dilution factor* Significant decrease.	All lung volumes, except for residual volume showed no significant change. No significant change in any of the flow rates.
Guyatt et al., 1970, England (*100*).	710 subjects; 508 smoked between measures 202 did not smoke.	A. Body plethysmography. B. 1 cigarette. C. Undefined.	*Bronchoconstriction* Significant increase with smoking.			On the average, nonsmokers and ex-smokers showed bronchodilation and smokers showed bronchoconstriction. The authors postulate that the result among nonsmokers is due to the release of adrenal hormones in these subjects.

[1] All the experiments listed concern studies of pulmonary function before and after smoking the epecified number of cigarettes (unless otherwise specified).

TABLE 12.—*Experiments concerning the effect of cigarette smoke on human and animal pulmonary clearance*

Author, year, country, reference	Subjects	Method	Results	Comments
Laurenzi et al., 1963, U.S.A. (*149*).	Swiss-Webster male mice.	Mice exposed to aerosol of *S. aureus* and sacrificed at intervals following exposure to various stimuli.	Significant increase in *S. aureus* retention in mice exposed to: (a) hypoxia—retention ratio 2.5 (10 percent 0_2). (b) cigarette smoke—retention ratio 4.5.	
LaBelle et al., 1966, U.S.A. (*145*).	Albino female rabbits.	Silver iodide or colloidal gold intratracheally.	17–30 hours of exposure to cigarette smoke caused no change in pulmonary clearance as compared with controls breathing room air.	
Bair and Dilley, 1967, U.S.A. (*23*).	Sprague-Dawley female rats, male beagle dogs.	Radioactive aerosol. Radioactive aerosol.	Acute exposure to cigarette smoke had no gross effect on clearance. Chronic exposure to cigarette smoke (up to 18–20 cigarettes/7 hour day/5 day week for up to 420 days) had no observable effects. The authors noted, however, that normal clearance rates were too low to reflect anything but complete cessation.	

Author, year, country, reference	Subjects	Method		*Number of subjects*	*Average age*	*50 percent clearance time (minutes)*	*90 percent clearance time (minutes)*	Comments
Albert et al., 1969, U.S.A. (*2*).	36 subjects undergoing 117 experiments.	Radioactive tagged $Fe0_2$ particles measured with Scintillation counter.	Nonsmokers	9	28	88	357	† Approximate values. None of 9 nonsmokers had 50 percent times over 200 minutes or 90 percent times over 600 minutes while 6/14 smokers exceeded both these limits.
			All smokers	14	33	172	†496	
			20–29 cigarettes/day	7	29	191	†519	
			30–40 cigarettes/day	7	36	153	†474	
			Uranium miners	3	52	310	580	
			Cigar and pipe smokers	4	46	87	376	
			Emphysema patients	2	66	330	575	

TABLE 12.—*Experiments concerning the effect of cigarette smoke on human and animal pulmonary clearance (cont.)*

Author, year, country, reference	Subjects	Method	Results						Comments
Albert et al., 1969, U.S.A. (*5*).	*Donkeys exposed* to cigarette smoke by nasal catheter.	Radioactive tagged $Fe0_2$ particles measured with Scintillation counter.	*Average number cigarettes in 2-hour period*	*Percent clearance*		*Halftime clearance*		*Tracheal transit time*		*Those donkeys exposed* to the greatest amount of smoke showed residual impairment of clearance for at least 2 months after acute exposure.
				Control	*Cigarette*	*Control*	*Cigarette*	*Control*	*Cigarette*	
			18–24	58	69	1.2	1.9	0.6	1.2	
			36	58	64	1.0	3.4	0.4	5.8	
Holma, 1969, U.S.A. (*125*).	Rabbits (anesthetized).	Cr^{51} monodisperse polystyrene aerosol.	Exposure to fresh cigarette smoke (1.5 cc. puffs, 40 puffs/8 minutes) caused a "significant" increase in lung retention 10 minutes following cessation of exposure.							

originate in tobacco smoke. The authors suggested that the tobacco smoke may have induced abnormalities in the mitochondria of the macrophage. In a study of pulmonary macrophages harvested by endobronchial lavage from smokers and nonsmokers, Pratt, et al. (*187*) observed that the macrophages of smokers contained an abnormal pigment.

These studies indicate that the function of pulmonary clearance carried on by the macrophage and ciliary systems is adversely affected by cigarette smoke.

Studies Concerning the Surfactant System

The surfactant system of the lung consists of various biologically active compounds such as phospholipids and mucopolysaccharides which are present in the alveolar lining. Normal pulmonary function is influenced and partly determined by the integrity of this system (*203*). The purpose of the surfactant system is to maintain the proper amount of surface tension in the alveoli so that the expansion and contraction of the alveoli are facilitated.

Studies concerning the effect of cigarette smoke upon the surfactant system and the surface tension of the pulmonary alveoli are presented in table A14. Exposure of rat and dog lung extracts to cigarette smoke has been found to induce a notable decrease in the maximal surface tension demonstrated by the extracts (*94, 165, 224*). Cook and Webb (*57*) observed that surfactant activity was diminished in smokers and in patients with pulmonary disease when compared with healthy nonsmokers.

Scarpelli (*203*) in a recent review, concluded that the lowering of maximal surface tension by cigarette smoke has been demonstrated reasonably well. The relationship of these findings to the pathogenesis of emphysema is unclear at this time.

OTHER RESPIRATORY DISORDERS

Infectious Respiratory Diseases

Several studies have examined the question of whether cigarette smokers are at an increased risk of developing infectious respiratory and bronchopulmonary disease. Table A15 presents a summary of these studies. Lowe (*157*) observed an excess of smokers among 705 tuberculosis patients, but Brown and Campbell (*43*) in a similar study found that the difference was not present when the cases and controls were matched for alcohol intake. More recent studies have been concerned with the frequency of upper respiratory infections among groups of smokers and nonsmokers. A number of investigators (*108, 181, 183*) have reported increased

rates of respiratory illnesses among smokers. Finklea, et al. (*83*) studied a male college population (prospectively) during the 1968–69 influenza epidemic. They found that smokers of all amounts experienced more clinical illness than did nonsmokers and that this relation was dose-dependent. Similarly, smokers required more bed rest than nonsmokers.

A survey conducted by the National Center for Health Statistics (*220*), involving approximately 134,000 persons, showed that male cigarette smokers reported 54 percent more cases of acute bronchitis than males who had never smoked cigarettes, while female smokers reported 74 percent more acute bronchitis than did females who had never smoked. Male cigarette smokers reported 22 percent more cases of influenza than did males who had never smoked cigarettes, while the female smokers reported an excess of 9 percent.

Experimental evidence in support of this relationship has been noted by Spurgash, et al. (*211*). Mice were challenged with *Klebsiella pneumoniae* or *Diplococcus pneumoniae* before or after a single exposure to cigarette smoke. They observed that those animals exposed to smoke exhibited a decrease in resistance to respiratory infection, as shown by an increase in mortality and a decrease in survival time. Preexposure to cigarette smoke was found to have no significant effect on resistance of mice to influenza infection initiated by aerosol exposure. However, exposure of infected mice to smoke resulted in significantly higher mortality, thus suggesting that cigarette smoke can aggravate an existing respiratory viral infection.

In the light of the experimental evidence presented above concerning the effect of cigarette smoke on pulmonary clearance, phagocytosis, and ciliary function, it seems reasonable to conclude that such changes in tracheobronchial physiologic function would predispose a person to respiratory infections or aggravate already existing ones.

Further evidence is derived from the work of Henry, et al. (*109*) and Ehrlich, et al. (*75*). These investigators exposed squirrel monkeys to atmospheres containing 10 and 5 p.p.m. of nitrogen dioxide. They observed that this exposure increased the susceptibility of the animals to airborne *Klebsiella pneumoniae* as demonstrated by increased mortality and reduced lung clearance of viable bacteria. Infectious challenge with influenza virus 24 hours before exposure to 10 p.p.m. was fatal to all monkeys within three days. Infected controls showed symptoms of viral infection but did not succumb to the infection. The extent to which the various oxides of nitrogen present in cigarette smoke contribute to the increased susceptibility to respiratory disease noted in smokers is presently undefined.

Postoperative Complications

Several studies have been published which examine the questions of whether smokers run an increased risk of developing postoperative pulmonary complications over nonsmokers undergoing similar operations.

Morton (*173*) reported on a study of more than 1,100 patients undergoing abdominal operations in which he found that cigarette and mixed smokers were significantly more likely to develop bronchitis, bronchopneumonia, or atelectasis during the postoperative period than nonsmokers (table A16).

Wiklander and Norlin (*229*) examined the incidence of postoperative complications in 200 patients undergoing laparotomy in the winter months when it was expected that pulmonary complications would be at their maximum. These authors found no significant differences between the frequency of complications in smokers and nonsmokers. No information about the definition of a smoker and no data on dosage of tobacco smoke were reported.

Piper (*186*) observed the prevalence of postoperative pulmonary complications in 150 patients undergoing laparotomy. Of the total sample, 66.7 percent developed pulmonary complications during the first postoperative week. All patients considered in the statistical analysis as having pulmonary complications had radiographic evidence of disease. Of the cigarette smokers, 73.5 percent had complications as compared to 55.5 percent of the nonsmokers. When the smokers were divided according to dosage, heavy smokers being those consuming more than 10 cigarettes per day for the previous six months, 55 percent of light smokers and 88 percent of heavy smokers were considered to have postoperative complications. Piper also reported that stopping smoking for up to four days preoperatively had no apparent effect on the incidence of complications.

Wightman (*228*) reported on the incidence of postoperative pulmonary complications in 455 patients undergoing abdominal operations and in 330 patients undergoing other operations. Of the cigarette smokers, 14.8 percent developed complications as compared to 6.3 percent of the nonsmokers. The substantial difference between these figures and those of Piper (*186*) is due to the latter's use of radiographic criteria alone. Wightman utilized only clinical criteria.

Morton (*172*) has recently reported a study of postoperative hypoxemia in 10 patients, 5 of whom were cigarette smokers. Four of the smokers had chronic bronchitis. He found that the smokers had a more pronounced decrease in arterial oxygen saturation, persisting into the second postoperative day (table A17).

In summary, the majority of studies so far reported indicate that cigarette smokers run a higher risk of developing postoperative pulmonary complications than do nonsmokers, corroborating a long-held clinical impression. The risk of developing such complications appears to increase with increasing dosage of cigarette smoke.

SUMMARY AND CONCLUSIONS

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

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

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

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

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

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

7. The results of experiments in both animals and humans have demonstrated that the inhalation of cigarette smoke is associated with acute and chronic changes in ventilatory function and pulmonary histology. Cigarette smoking has been shown to alter the mechanism of pulmonary clearance and adversely affect ciliary function.

8. Pathological studies have shown that cigarette smokers who die of diseases other than COPD have histologic changes charac-

teristic of COPD in the bronchial tree and pulmonary parenchyma more frequently than do nonsmokers.

9. Respiratory infections are more prevalent and severe among cigarette smokers, particularly heavy smokers, than among nonsmokers.

10. Cigarette smokers appear to develop postoperative pulmonary complications more frequently than nonsmokers.

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BRONCHOPULMONARY

APPENDIX TABLES

TABLE A2.—*Smoking and chronic obstructive pulmonary disease symptoms*[1]*—percent prevalence*

(Numbers in parentheses represent total number of individuals in particular smoking group)

SM = Smokers. NS = Nonsmokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	Cough	Sputum production	Breathlessness or dyspnea	Chest illnesses	Other	Comments
Short et al., 1939, U.S.A. (*206*).	2,031 male and female insurance policy holders.	NS ..... 1.6 (496) SM 6.4 (1,293)			NS .....10.9 SM 18.0		Chest illnesses as represented by frequent colds.
Oswald and Medvei, 1955, England (*178*).	3,602 male and 2,242 female clerical workers 40–65 years of age.					*Chronic Bronchitis* *Males* NS .....15.8 (474) SM .....18.4 (1,940) *Females* NS .....12.1 (619) SM 18.8 (579)	Chronic bronchitis defined by habitual cough and sputum production.
Phillips et al., 1956, U.S.A. (*185*).	1,274 male factory workers without overt pulmonary disease or heart failure.	NS ..... 2.0 (451) SM 51.0 (823)					
Higgins 1957, England (*112*).	301 male and 280 female rural dwellers 25–74 years of age.		*Cough and sputum* *Males* NS ..... 7.1 (28) SM .....53.9 (222) *Females* NS ..... 4.5 (176) SM 17.2 (93)	*Males* NS ..... 7.1 SM .....19.8 *Females* NS .....21.6 SM 9.7	*Males* NS ..... 3.6 SM .....17.1 *Females* NS ..... 9.7 SM 15.1	*Chronic Bronchitis* *Males* NS ..... 3.6 SM ..... 9.9 *Females* NS ..... 3.4 SM 8.6	

TABLE A2.—*Smoking and chronic obstructive pulmonary disease symptoms*[1]*—percent prevalence (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)

SM = Smokers. NS = Nonsmokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	Cough	Sputum production	Breathlessness or dyspnea	Chest illnesses	Other	Comments
Higgins and Cochran, 1958, England (*114*).	94 males and 92 females randomly chosen (members of an agricultural community.)		*Females* *Cough and sputum* NS ..... (6) SM .....24.0 (75) NS ..... 3.1 (64) SM 3.0 (20)	*Males* NS .....33.3 SM .....29.3 *Females* NS .....45.3 SM 20.0	*Males* NS ..... 0.0 SM ..... 16.0 *Females* NS ..... 10.9 SM 10.0	*Chronic bronchitis* *Males* NS ..... 0.0 SM ..... 6.7 *Females* NS ..... 0.0 SM 5.0	
Edwards et al., 1959, England (*74*).	1,737 male outpatients on lists of general practitioners >60 years of age.					*Chronic bronchitis* NS .....16.6 (151) Cigarettes 29.7 (779) 1–9 .... 23.4 (235) 10–19 .... 31.2 (369) >20 ..... 33.7 (175) Pipe 18.5 (340)	
Flick and Paton, 1959, U.S.A. (*86*).	222 male patients not suffering from overt cardiopulmonary disease, 20–90 years of age.	NS .....10.0 (51) SM 55.0 (157)	NS .....25.0 (49) SM 65.0 (156)		NS ..... 30.0 (47) SM 60.0 (138)		
Higgins et al., 1960, England (*116*).	776 males in various occupations 25–64 years of age.		*Cough and sputum* SM ..... 7.1 (85) NS 36.9 (575)	NS ..... 9.4 SM 24.9	NS ..... 7.1 SM 20.2	*Chronic bronchitis* SM ..... 14.3 NS 3.5	

TABLE A2.—*Smoking and chronic obstructive pulmonary disease symptoms*[1]*—percent prevalence (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)

SM = Smokers. NS = Nonsmokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	Cough	Sputum production	Breathlessness or dyspnea	Chest illnesses	Other	Comments
Higgins, 1959, England (*113*).	393 males in various occupations 55–64 years of age.		*Cough and sputum* NS ..... 6.1 (33) 1–14 g./day 9.7 (173) >15 .....42.3 (142)	NS ..... 18.2 1–14 g./day 30.1 >15 ..... 33.8	NS ..... 3.0 1–14 g./day 23.7 >15 .....23.9	*Chronic bronchitis* NS ..... 0.0 1–14 g./day 13.9 >15 ..... 17.6	Chronic bronchitis defined as persistent sputum and at least 1 chest illness in past 3 years. Tobacco gram equivalents are: 1 cigarette = 1 gram, 1 cigar = 2–5 grams, 1 pipe = 10–25 grams.
Liebeschuetz, 1959, England (*156*).	147 male soldiers 20–30 years of age.	NS ..... 0.0 (52) SM 13.0 (83)					
Ashford et al., 1961, England (*11*).	4,014 male coal workers.					*Respiratory symptoms* NS ..... 10.3 (677) EX ..... 19.5 (123) Cigarettes 21.1 (1,504) Pipe only 35.1 (202) Cigarettes and pipe 37.1 (90) All SM .. 21.7 (3,214)	Respiratory symptoms—"bronchitis and/or asthma". No dose relationship found.

TABLE A2.—*Smoking and chronic obstructive pulmonary disease symptoms*[1]*—percent prevalence (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)

SM = Smokers. NS = Nonsmokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	Cough	Sputum production	Breathlessness or dyspnea	Chest illnesses	Other	Comments
Bower, 1961, U.S.A. (41).	95 male and 77 female bank employees 40-70 years of age.	NS ..... 4.1 (49) SM .....27.6 (76) Pipe, cigar .. (13)	NS .....20.4 SM .....34.2 Pipe, cigar 15.4		NS .....34.7 SM .....38.2 Pipe, cigar 53.9		Chest illness—chest colds during each of last 2 winters.
Fletcher and Tinker, 1961, England (85).	303 male London transport employees 40-50 years of age.	NS .... (80) 1-14 g./day 15.5 (150) >15 .....27.3 (110)	NS ....., 8.7 1-14 g./day ..29.9 >15 .....30.9	NS .... 1-14 g./day .. 8.2 >15 ..... 8.0	NS ..... 4.8 1-14 g./day 8.2 >15 ....10.7		
Read and Selby, 1961, Australia (191).	170 male and 132 female individuals interviewed in an out-patient clinic (not all patients).	*Males* NS ..... 4.4 SM .....23.1 EX .....21.2 *Females* NS ..... 4.9 SM 18.6					
Balchum et al., 1962, U.S.A. (24).	1,451 male light industry employees in California.	NS .....10.2 (258) SM .....23.3 (1,108) <1 pack-year .....11.0 (257) 1- 9 .....17.0 (263) 10-19 .....25.0 (303) 20-29 .....21.0 (236) 30-39 .....28.0 (144) 40-49 .....39.0 (92) 50-59 .....34.0 (29) >60 .....50.0 (24)	NS ....., 11.0 SM .....30.4 <1 pack-year .....12.0 1- 9 .....18.0 10-19 .....32.0 20-29 .....34.0 30-39 .....40.0 40-49 .....37.0 50-59 .....46.0 >60 .....62.0	NS ..... 9.8 SM .....14.5 <1 pack-year .10.0 1- 9 .....12.0 10-19 .....11.0 20-29 .....18.0 30-39 .....21.0 40-49 .....13.0 50-59 .....38.0 >60 .....29.0			

TABLE A2.—*Smoking and chronic obstructive pulmonary disease symptoms*[1]*—percent prevalence (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)

SM = Smokers. NS = Nonsmokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	Cough	Sputum production	Breathlessness or dyspnea	Chest illnesses	Other	Comments
Boucot et al., 1962, U.S.A. (*36*).	6,137 males enrolling in pulmonary neoplasm project.	NS .....13.0 (806) SM 31.5 (5,331)					
Ferris et al., 1962, U.S.A. (*82*).	90 male and 71 female flax mill-workers.					*Chronic Nonspecific Respiratory Disease* *Males* *Females* NS ..15.0 (20) 10.0 (60) EX ..12.5 (16) .. 1-20 .27.3 (22) .. >20 .53.1 (32) 50.0 (4)	
Ferris and Anderson, 1962, U.S.A. (*81*).	542 male and 625 female residents of New Hampshire town chosen by random sampling of census.					*Chronic bronchitis* *Males* NS ..... 13.8 (125) EX .....11.9 (77) Cigarettes 40.3 (340) 1-10 .....29.8 11-20 .....34.2 21-30 .....42.3 31-40 .....61.1 >41 .....76.3 *Females* NS ..... 9.4 (378) EX .....10.8 (37) Cigarettes 19.8 (208) 1-10 .....13.1 11-20 .....22.2 21-30 .... 31-40 .....27.3 >41	Age-specific rates.

TABLE A2.—*Smoking and chronic obstructive pulmonary disease symptoms*[1]*—percent prevalence (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)

SM = Smokers. NS = Nonsmokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	Cough	Sputum production	Breathlessness or dyspnea	Chest illnesses	Other	Comments
Goldsmith et al., 1962, U.S.A. (95).	3,381 active or retired longshoremen.					*Respiratory conditions* NS ..... 31.4 (744) Moderate/heavy smokers 43.0 (1,238)	
Coates et al., 1965, U.S.A. (53).	1,342 male and 242 female Detroit post office employees.		NS .....11.2 (747) 1-14 ...12.7 (266) (not sig.) 15-24 ...27.5 (402) (p<0.001) >25 ....36.4 (170) (p<0.001)	NS ...14.7 1-14 .28.2 (p<0.001) 15-24 .30.7 (p<0.001) >25 ..34.1 (p<0.001)		*Cough and chronic phlegm* NS ..... 4.0 1-14 .... 5.3 (not sig.) 15-24 .... 17.2 (p<0.001) >25 ..... 26.3 (p<0.001)	Current smoking data.
Deane et al., 1965, U.S.A. (67).	508 telephone company workers.					*Persistent cough, phlegm, dyspnea* NS ..... 4.5 (200) Current cigarette smokers 15.9 (308)	NS includes ex-smokers, pipe, and cigar smokers.
Huhti, 1965, Finland (126).	653 male and 823 female residents of a Finnish communal region, 40-64 years of age.	*Males* NS ..... 4.1 (122) EX ..... 8.5 (141) 1-14 .....31.5 (108) 15-24 .....40.8 (191) >25 .....42.4 (85) *Females* NS ..... 4.5 (709) EX .....13.3 (30) 1-14 .....10.4 (77) 15-24 .....43.0 (6) >25 ..... (1)	*Males* NS .....10.7 EX .....17.7 1-14 .....38.0 15-24 .....42.9 >25 .....42.4 *Females* NS ..... 5.9 EX .....13.3 1-14 .....10.4 15-24, >25 .....57.0	*Males* NS .....15.6 EX .....24.8 1-14 .....25.0 15-24 .....26.2 >25 .....31.8 *Females* NS .....29.2 EX .....33.3 1-14 .....14.3 15-24, >25 .....14.0		*Chronic bronchitis* *Males* NS ..... 5.7 EX .....16.3 1-14 .... 38.0 15-24 ....41.4 >25 .....40.0 *Females* NS ..... 4.6 EX ..... 13.3 1-14 .... 10.4 15-25, >25 .....57.0	Ex-smokers represent those who have stopped smoking for more than 1 month. Dyspnea Grade II only.

TABLE A2.—*Smoking and chronic obstructive pulmonary disease symptoms*[1]*—percent prevalence (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)

SM = Smokers. NS = Nonsmokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	Cough	Sputum production	Breathlessness or dyspnea	Chest illnesses	Other	Comments
Wynder et al., 1966 U.S.A. (*238*).	315 male patients in New York City and 315 male patients in California.	*New York City* NS .....14.0 (44) Pipe, cigar 33.0 (54) Cigarettes: 1–10 ...45.0 (44) 10–20 ...46.0 (88) >20 ....67.0 (85) *California* NS .....22.0 (69) Pipe, cigar 30.0 (32) Cigarettes: 1–10 ...45.0 (54) 10–20 ...74.0 (91) >20 ....74.0 (69)					
Freour et al., 1966 France (*92*).	1,055 randomly chosen males in Bordeaux 30–70 years of age.					*Clinical signs of bronchitis and respiratory insufficiency* NS ..... 25.4 (45) SM 54.4 (478)	
Haynes, et al., 1966 U.S.A. (*108*).	179 male preparatory school students 14–19 years of age.					*Average number of severe respiratory illnesses per 10 students (adjusted for age)* NS ..... 0.36 All smokers 2.30 Heavy SM 3.34	Heavy smoker—more than 10 cigarettes per day.

TABLE A2.—*Smoking and chronic obstructive pulmonary disease symptoms*[1]*—percent prevalence (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)

SM = Smokers. NS = Nonsmokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	Cough	Sputum production	Breathlessness or dyspnea	Chest illnesses	Other	Comments
Densen et al., 1967, U.S.A. (*68*).	5,313 male and 7,291 female postal and transit workers.	*Postal* NS ..... 7.0 (903) Pipe, cigar 12.4 (628) Cigarettes only ....27.0(2,687) *Transit* NS ..... 6.4(1,012) Pipe, cigar 10.5 (765) Cigarettes only ....23.5(3,745)	*Postal* 13.1 17.4 28.9 *Transit* 9.5 14.1 23.7	*Postal* 19.8 24.8 31.7 *Transit* 11.7 14.2 21.9			Dyspnea represented by Grade II only.
Higgins et al., 1968, U.S.A. (*118*).	926 white male residents of Marion County, West Virginia, 26–69 years of age.	NS .....15.4 (162) SM .....47.2 (513) EX 19.3 (144)	NS .....31.1 SM .....46.2 EX 28.5	NS ..... 5.0 SM .....10.7 EX 16.8			
Holland and Elliott, 1968, England (*121*).	9,786 male and female school children.	*Males* *Females* *Males* *Females* NS ..... 3.8(1,000) 3.2(3,137) 2.4 2.1 SM ..... 6.3(1,098) 6.3 (554) 6.1 8.3 EX ..... 2.9(1,782) 4.3(1,151) 3.9 4.2 <1 cigarette/day .....5.8(876) 5.8 1–2 .....6.5(417) 8.4 3–4 .....5.6(124) 8.1 >5 .....9.9(142) 18.3					

TABLE A2.—*Smoking and chronic obstructive pulmonary disease symptoms*[1]*—percent prevalence (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)

SM = Smokers. NS = Nonsmokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	Cough	Sputum production	Breathlessness or dyspnea	Chest illnesses	Other	Comments
Gandevia 1969 Australia (*93*).	762 male and 1,304 female patients from 13 general practices in all parts of Australia.	*Males* NS .....10.3 (234) SM .....51.3 (528) *Females* NS .....10.5 (857) SM 37.4 (447)					Productive cough upon request.
Rimington 1969 England (*193*).	41,729 male and 22,295 female persons participating in mass miniature radiography screening.					*Age-adjusted total prevalence of chronic bronchitis* *Males* NS ..... 5.1 (9,055) EX ..... 9.8 (6,510) Pipe ..... 9.0 (2,921) Cigarettes . (23,243) 1- 9 ..... 9.1 10-19 .... 15.0 >20 .....20.6 *Females* NS ..... 3.4 (12,361) EX ..... 3.8 (959) Pipe .... 0.0 Cigarettes (8,985) 1- 9 ... 5.1 10-19 ... 10.6 >20 ..... 18.5	Cigarette dosage gradient significant to $p<0.001$.
Wilhelmsen et al., 1969, Sweden (*231*).	313 males 50–54 years of age randomly sampled from population of Göteborg.					*Chronic bronchitis* NS ..... 1.0 (88) EX ..... 3.0 (67) 1-14 grams/day ... 5.0 (94) >15 ..... 17.0 (64)	

TABLE A2.—*Smoking and chronic obstructive pulmonary disease symptoms*[1]*—percent prevalence (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)

SM = Smokers. NS = Nonsmokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	Cough	Sputum production			Breathlessness or dyspnea	Chest illnesses	Other	Comments
Lambert and Reid, 1970, England (*148*).	9,975 male and female responders to a postal survey (4,688 males and 5,287 females 35-69 years of age).	*Persistent cough and phlegm*							
			Males						
		Age 35-45	*Age 45-55*	*Age 55-65*	*Age 65-69*				
		NS ..... 7(227)	6(200)	11(171)	7 (61)				
		EX ..... 7(303)	11(358)	15(335)	18(148)				
		<20 ....15(521)	22(488)	30(490)	37(139)				
		20 .....23(191)	28(204)	32(140)	38 (37)				
		>20 ....27(148)	28(136)	42(121)	25 (12)				
			Females						
		NS ..... 3(600)	4(637)	5(925)	6 (21)				
		EX ..... 3(127)	8(128)	7 (94)	7 (41)				
		<20 .... 9(602)	13(472)	16(306)	11 (65)				
		20 .....16(128)	27(122)	31 (77)	14 (7)				
		>20 ....23 (22)	26 (39)	43 (7)	.. (1)				
Lefcoe and Wonnacott, 1970, Canada (*151*).	310 male physicians in London and Ontario, 25-74 years of age.							*Age-standardized rates of chronic respiratory disease* NS ..... 1.0 (88) EX ..... 6.0 (61) SM .....34.0 (101) Pipe, cigar ..12.0 (33)	Excluded from ex-smokers are those cigarette smokers who now smoke pipes or cigars.

[1] Data collected by either direct interview, questionnaire, review of medical records and/or medical examination.

TABLE A2a.—*Smoking and chronic obstructive pulmonary disease symptoms*[1]*—percent prevalence*

(Numbers in parentheses represent total number of individuals in particular smoking group)

SM = Smokers. NS = Nonsmokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of popuation	Cough		Bronchitis		Comments
				Explanation of analyses for respiratory symptom prevalence:		
Cederlof et al., 1966, Sweden (46).	9,319 twin pairs registered in Sweden of 12,889 available.	*Observed/ expected cases*	*Hypermorbidity ratio*	*Observed expected cases*	*Hypermorbidity ratio*	All ex-smokers included with smokers. MZ—monozygotic pairs DZ—dizygotic pairs Author concludes that since hypermorbidity for smoking persists in smoking-discordant MZ population, a casual relationship of smoking and broncho-pulmonary symptoms is supported.
		Group A:				
		Males 393/151.9	2.6	157/50.8	3.1	Group A analysis—using each firstborn twin as one group in an unmatched relationship to each secondborn twin. Group B analysis—using each twin set as matched pair. All comparisons in Groups A and B are between smoking-discordant pairs.
		Females 136/ 49.4	2.8	43/11.2	3.8	
		Group B SM/NS:				
		MZ Males 14.6/7.7	1.9	6.6/ 1.1	6.0 (274)	
		Females ... 13.6/7.6	1.8	3.0/ 2.3	1.33(264)	
		DZ Males 12.3/5.5	2.25	4.5/ 1.8	2.54(733)	
		Females ... 14.5/5.7	2.57	5.5/ 1.8	3.0 (663)	
Cederlof et al., 1969, U.S.A. (45).	4,379 twin pairs (all U.S. veterans) in U.S. National Academy of Sciences Twin Registry (of 9,000 available).	*Prevalence of respiratory symptoms*				No ex-smokers included in Group B analysis. The authors conclude that the data indicate a strong probability of a causal connection with smoking. Even these symptoms, however, seem to be influenced by genetic factors.
		Group A:				
		NS 4.3	4.3		1.6	Group A—as above.
		1-10 ..... 6.4	6.4		2.7	Group B—as above.
		11-30 .....15.3	15.3		8.0	
		>31 .....27.7	27.7		16.8	
		Pipe, cigar 7.1	7.1		2.7	
		Group B:	*NS*	*SM*	*NS*	*SM*
		MZ 2.4	5.4		1.8	4.8
		DZ 2.0	9.8		1.6	9.1

[1] Data collected by either direct interview, questionnaire, review of medical records and/or medical examination.

TABLE A3.—*Smoking and ventilatory function*

(Numbers in parentheses represent total number of individuals in particular smoking group)
NS = Nonsmokers. SM = Smokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	MBC	EFR	FEV	VC	Miscellaneous	Comments
Chivers, 1969, England (*58*).	463 male employees of alkaline industry plant.		*Height-in-inches*				†Mean EFR in liters per minute. Regression analysis of data revealed a significant relationship between smoking and decreasing function.
		Cigarettes/day:	*64''*	*66''* *68''* *70''*			
		0–5	†97 (28)	91 (35) 108 (31) 101 (21)			
		6–20	89 (50)	88 (75) 101 (112) 109 (75)			
		>20	63 (6)	88.5 (9) 92.5 (9) 113 (12)			
Higgins et al., 1959, England (*116*).	773 males in various occupations (25–34 and 55–64 years of age).		*25–34*	*55–64*			$FEV_{0.75}$ expressed as mean indirect MBC.
		NS	145 (66)	101 (29)			
		EX	143 (31)	89 (62)			
		1–14 grams	140 (193)	87 (157)			
		>15 grams	133 (89)	80 (186)			
Wilson et al., 1960 U.S.A. (*232*).	28 male residents of Dallas, Texas, former rural dwellers; matched for body surface, age, and height.				*RV/TLC*		
					NS 5.59 (14)	NS 21.1	
					SM ..... ‡4.44 (14)	SM .....‡27.01	

TABLE A3.—*Smoking and ventilatory function (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)
NS = Nonsmokers. SM = Smokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	MBC	EFR	FEV	VC	Miscellaneous	Comments
Ashford et al., 1961, Scotland (*11*).	4,014 male coal workers at 3 Scottish collieries.			$FEV_{1.0}$ Age: NS SM <21–30 4.09 (103) 3.96 (280) 21–30 . 3.86 (182) 3.77 (555) 31–40 . 3.44 (138) 3.38 (777) 41–50 . 3.04 (110) 2.96 (755) 51–60 . 2.71 (102) 2.56 (610) >60 . . . 2.38 (42) 2.21 (237)			Data represent results after correction for sitting height. SM includes pipe smoker. Data on ex-smoker not included. $FEV_{1.0}$ found significant; lower for SM than NS.
Fletcher and Tinker, 1961, England (*85*).	363 male London transport employees.		*Mean peak EFR* NS . . . . . 570 (30) 1–14 grams 537 (156) >15 grams 528 (116) EX 555 (61)				
Franklin and Lowell, 1961, U.S.A. (*87*).	213 male factory workers 40–60 years of age.			$FEV_{1.0}$ $FEV_{0.25}^{0.75}$ $FEV_{0.50}^{0.75}$ Heavy 2,670 3,011 2,710 Light . . 3,703 (59) Light [2]2,489 [2]2,666 [2]2,284 Heavy . [1]3,578 (104)			Heavy smoker represents an amount equal to or more than 30 pack years.

TABLE A3.—*Smoking and ventilatory function (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)
NS = Nonsmokers. SM = Smokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	MBC	EFR	FEV	VC	Miscellaneous	Comments
Balchum et al., 1962, U.S.A. (*14*).	1,461 male employees in California light industry.		*MMEFR* NS ..... 16.5 (38) Pack/year: <1 ..... 15.0 (257) 1–9 .... 10.0 (263) 10–19 ... 10.0 (303) 20–29 ... 19.0 (236) 30–39 ... 33.0 (144) 40–49 ... 38.0 (92) 50–59 ... 55.0 (29) >60 ..... 71.0 (24)	7.8 (19) 8.0 6.0 12.0 24.0 26.0 40.0 46.0 62.0			Data for: MMEFR given as percent of individuals with a value of <500 L/M; $FEV_{1.0}$ given as percent of individuals with value of <70 percent of expected.
Goldsmith et al., 1962, U.S.A. (*95*).	3,311 active or retired longshoremen.		*MEFR* NS ..... 313.63 (250) Pipe, cigar 299.26 (125) EX ..... 295.23 (102) Cigarettes/day: ≦20 ..... 309.73 (144) 20–40 ... 303.44 (346) ≧40 ..... 307.63 (57)	*$FEV_{1.0}$* 2.99 2.80 2.84 2.89 2.91 2.90			Authors concluded that cigarette smoke was found to have a slight effect on pulmonary function.
Martt, 1962, U.S.A. (*161*).	73 healthy medical personnel without significant age difference between smokers and nonsmokers.					*D_LCO* NS ..... 33.10 (30) SM <5 years .[2]28.40 (8) 5–10 years ...[3]28.20 (10) >10 years ...[4]24.90 (25)	Smokers defined as those smoking >20 cigarettes/day for varying periods.

TABLE A3.—*Smoking and ventilatory function (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)

NS = Nonsmokers. SM = Smokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	MBC	EFR	FEV	VC	Miscellaneous	Comments
Revotskie et al., 1962, U.S.A. (*192*).	1,130 male and 1,813 female residents in Framingham participating in the prospective study.			*$FEV_{1.0}$* *Males* *Females* NS .....0.98 (55) 0.98(255) Cigarettes/day: 1–10 .0.97 (90) 0.99 (92) 10–29 .0.91(163) 0.93(157) >30 ..0.90 (81) 0.91 (22)			Data presented in terms of ratio of observed to predicted values.
Krumholz et al., 1964, U.S.A. (*140*).	18 physicians 24–37 years of age.		*MEFR* NS ..... 580 (9) SM ..... [1]590 (9)			*Mean D_L* *NS* *SM* Rest .....36 [1]31 Exercise: 2 minutes ..50 [1]41 4 minutes ..50 [1]48 8 minutes post exercise 39 [1]35	
Zwi et al., 1964, U.S.A. (*241*).	20 medical students or graduate physicians.	NS ... 187 (10) SM ...[1]193 (10)	*MMEFR* 4.84 [1]5.09	5.77 [1]5.53		Authors found a significant difference between SM and NS for RV/TLC, compliance, and nonelastic resistance.	
Coates et al., 1965, U.S.A. (*53*).	1,342 male and 242 female post office employees >40 years of age.			*$FEV_{1.0}$* *Timed VC*[1] *$FEV_{1.0}/VC$* Age: *NS* *>25 cig/day* *NS* *>25/day* *NS* *>25/day* 40–44 [1]2.99(186) 2.85 (69) 3.89 3.85 [1]0.77 0.74 45–49 [1]2.95(170) 2.64 (42) 3.92 3.83 [1]0.74 0.70 50–54 [1]2.75(115) 2.62 (22) 3.71 3.74 [1]0.74 0.70 55–59 [1]2.64 (64) 2.44 (18) 3.64 3.61 [1]0.74 0.68 60–64 [1]2.35 (53) 2.30 (8) 3.30 3.33 [1]0.72 0.70		

TABLE A3.—*Smoking and ventilatory function (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)
NS = Nonsmokers. SM = Smokers, EX = Ex-smokers.

Author, year, country, reference	Number and type of population	MBC	EFR	FEV	VC	Miscellaneous	Comments
Huhti, 1965, Finland (*186*).	653 male and 823 female residents of a rural region in Finland.		*PEFR*†	*$FEV_{1.0}$*‡	*Forced VC*‡		Pipe and cigar smokers not included. † Difference between NS and >25/day is significant for 45–49, 60–64 age groups. ‡ Trend is not statistically significant.
			Males / *Females*	*Males* / *Females*	*Males* / *Females*		
		NS	569(122) / 410(700)	3.46 / 2.42	4.40 / 3.18		
		EX	551(141) / 403 (80)	3.39 / 2.82	4.61 / 3.19		
		Cigarettes/day:					
		1–14	518(108) / 481 (77)	3.17 / 2.74	4.40 / 3.53		
		15–24	537(191) / 493 (7)	3.30 / 2.82	4.61 / 3.50		
		>25	517 (85) / 493 (7)	3.08 / 2.82	4.26 / 3.50		
Krumholz et al., 1965, U.S.A. (*148*).	20 male medical students or graduate physicians.					*Pulmonary compliance* NS .....0.241(10) SM .....[3]0.177(10) *Compliance/FRC* NS .....0.054 SM .....[3]0.042	Mean body surface area for 2 groups was not significantly different. Smokers are those with equal to or greater than 5 pack year history.
Rankin et al., 1965, U.S.A. (*189*).	125 males without a past history of respiratory disease 20–63 years of age.	NS ... 118.1 (68) SM ...[1]111.7 (57)	*$FEV_{1.0}$* NS .....106.6 SM .....[1]102.7			*D_L* NS ....81.1 SM ...[2]26.9 *D_L/alveolar volume* 8.22 [4]4.96	NS includes pipe and cigar smokers and ex-smokers of greater than 1 pack year. D_L values have been corrected for COHb.

TABLE A3.—*Smoking and ventilatory function (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)
NS = Nonsmokers. SM = Smokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	MBC	EFR	FEV	VC	Miscellaneous	Comments
Edelman et al., 1966, U.S.A. (*73*).	410 male community dwellers 20–103 years of age.	NS ..... 164(152) Current cigarette smokers. . [a]151(118) EX ..... 157 (98) Pipe, cigar .. 167 (47)	7.89 7.36 8.09 8.20	*FEV*$_{1.0}$ 2.83 [a]2.64 2.80 2.91	*Vital capacity* 4.93 [a]4.74 4.77 5.08		Ex-smokers of cigarettes only. Difference significant between NS and current cigarette smokers at $p<0.01$.
Peters and Ferris, 1967, U.S.A. (*182*).	124 male college age students.		*MEFR* NS .....[a]10.28 (41) Moderate . 10.06 (54) Heavy ..... 9.64 (29) EX 9.48 (10)	*FEV*$_{1.0}$ 4.68 4.59 4.43 4.74		*FEV*$_{1.0}$/*VC* [a]87.5 85.8 83.9 83.2	Heavy smoker refers to greater than or equal to 1 pack years. Moderate smoker includes pipe and cigar smokers. Difference between NS and heavy smoker is significant.
Higgins et al., 1968, U.S.A. (*118*).	926 white male residents of Marion County, West Virginia, 20–69 years of age.			*FEV*$_{1.0}$ NS ..... 3.64(160) EX ..... 3.25(148) Cigarette SM 3.48(511) 1–14 ..... 3.57 (88) 15–24 ..... 3.57(273) >25 ..... 3.30(150)			

TABLE A3.—*Smoking and ventilatory function (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)
NS = Nonsmokers, SM = Smokers, EX = Ex-smokers.

Author, year, country, reference	Number and type of population	MBC	EFR	FEV	VC	Miscellaneous	Comments
Sluis-Cremer and Sichel, 1968, South Africa (*208*).	533 white male factory workers over 35 years of age.			*35–44* *45–54* *>55*	$FEV_{1.0}$ *35–44* *45–54* *>65*		1 cigarette = 1 gram. 1 ounce tobacco = 26 grams. 1 cigar = 2 to 5 grams. † Derived slopes found significantly different from 0.
			NS	553(106) 527(101) 444(27)	3.70 3.22 2.76		
			Grams/day:				
			1–14	557 (26) 519 (17) 410 (7)	3.64 3.31 2.24		
			15–24	532 (94) 446 (35) 401(13)	3.66 2.94 2.28		
			>25	†528 (66) †494 (31) †380(10)	3.54 3.05 †2.12		
Stanescu et al., 1968, Rumania (*212*).	87 male bus drivers: 27 aged 20–25, 60 aged 40–60, all without respiratory symptoms.			$FEV_{1.0}$ *Younger* *Older*	*Younger* *Older*	*Nitrogen gradient* *Younger* *Older*	
			NS	4,470(14) 3,310(40)	5,125 4,290	1.63 2.49	
			SM	†4,500(13) †3,200(20)	†5,285 †4,290	†1.47 †3.77	
Densen et al., 1969, U.S.A. (*69*).	5,287 male postal and 7,213 male transit workers in New York City.			$FEV_{1.0}$ *Postal* *White*	*Non-white*		FEV expressed as standardized for specified postal and transit workers at age 45 and at sitting height of 35 inches. Includes mixed smokers.
			NS	3.29 (685)	3.05 (204)		
			All cigarette	3.11(2,340)	2.94 (768)		
			<25 grams/day	3.14(1,292)	2.95 (599)		
			≧25 grams/day	3.06(1,038)	2.93 (161)		
				Transit *White*	*Non-white*		
			NS	3.39 (620)	3.08 (298)		
			All cigarette	3.11(2,941)	2,99(1,041)		
			<25 grams/day	3.15(1,929)	3.00 (691)		
			≧25 grams/day	3.02(1,011)	2.95 (149)		

TABLE A3.—*Smoking and ventilatory function (cont.)*

(Numbers in parentheses represent total number of individuals in particular smoking group)

NS = Nonsmokers. SM = Smokers. EX = Ex-smokers.

Author, year, country, reference	Number and type of population	MBC	EFR	FEV	VC	Miscellaneous	Comments
Rankin et al., 1969, Australia (*190*).	60 male and 10 female patients with chronic alcoholism 26–66 years of age.			$FEV_{1.0}$ NS ..... 107.5 (12) SM 78.4 (58)			FEV expressed as percent of predicted value for age, sex, and height.
Wilhelmsen et al., 1969, Sweden (*231*).	313 male residents of Göteburg 50–54 years of age.			*PEFR* / $FEV_{1.0}$ / *VC* NS ..... 525(88) / 3.77 / 4.83 EX ..... 539(67) / 3.69 / 4.77 1–14 grams/day ..... 521(94) / 3.62 / 4.83 >15 grams/day ..... 492(64) / 3.39 / 4.56			1963 values only.
Lefcoe and Wynnacott, 1970, Canada (*151*).	310 male physicians of London, Ontario.		*MMFR* / $FEV_{1.0}$ NS ..... 4.09 (88) / 3.39 Cigarette smokers. 3.64(101) / 3.11 EX ..... 3.99 (61) / 3.38 Pipe, cigar 4.17 (33) / 3.17				MMFR has been standardized for age and height.

TABLE A3.—*Smoking and ventilatory function (cont.)*
(Numbers in parentheses represent total number of individuals in particular smoking group)
NS = Nonsmokers. SM = Smokers. EX = Ex-smokers.

Author, year, country, reference		FEV	Miscellaneous	Comments
Lundman, 1966, Sweden (*158*).	87 MZ and 62 DZ twin pairs selected from Swedish Twin-Pair Registry.	$\underline{FEV_{1.0}}$ Significant differences between smoking discordant twin pairs found for: 1. Group A MZ males and females. 2. Group B DZ males. 3. Group A DZ males.	$\underline{N_2 \text{ washout gradient}}$ Significant differences between smoking discordant twin pairs found for: Group B DZ males.	MZ = monozygotic. DZ = dizygotic. The author concludes that the degree of ventilation as measured by N_2 washout was correlated with cigarette consumption. The $FEV_{1.0}$ was significantly lower for smokers and there was a correlation with cigarette consumption. Explanation of analyses for respiratory symptom prevalence: Group A analysis—using each firstborn twin as one group in an unmatched relationship to each secondborn twin. Group B analysis—using each twin set as matched pair. All comparisons in Group A and B are between smoking-discordant pairs.

[1] Not significant (difference or trend).
[2] $p<0.05$
[3] $p<0.01$
[4] $p<0.005$
[5] $p<0.001$

TABLE A4.—*Glossary of terms used in tables and text on smoking and ventilatory function*

Symbol	Term	Volume or rate	Definition
MBC	Maximal breathing capacity.	Liters	The maximal volume of gas that can be breathed in one minute.
MVV	Maximal voluntary ventilation.		
EFR	Expiratory flow rate	Liters/minute	Rate of flow for a specified portion of a forced expiration (MMEFR—rate of flow measured for middle half of FVC).
PEFR	Peak expiratory flow rate.		
MEFR	Maximal expiratory flow rate.		
MMEFR	Maximal midexpiratory flow rate.		
FEV_t	Forced expiratory volume.	Liters	Volume expired within a specified time interval. ($FEV_{1.0}$—volume expired in first second of expiration.)
VC	Vital capacity	Liters	Maximal volume of a gas that can be expelled from the lungs by forceful effort following a maximal expiration.
FVC	Forced vital capacity.		
FEV_t/VC	Forced expiratory volume/vital capacity.	Percent	Volume of forced expiration (in time specified) related to vital capacity.
D_L	Pulmonary diffusing capacity.	ml/min/mmHg	The ability of a chosen gas to pass from the alveolus to within the pulmonary capillary.
N_2 washout	Nitrogen washout gradient.	Exponential curve.	The stepwise pulmonary alveolar clearance of a gas. (Slope of curve depends upon the uniformity and adequacy of ventilation of all parts of the lung.) It may be done as a single—or multiple—breath procedure.
	Compliance	Liters/CMH_20	Volume change of the lung produced by a unit pressure change.
RV	Residual volume	Liters	Volume of gas remaining in the lungs at the end of a maximal expiration.
TLC	Total lung capacity	Liters	Volume of gas contained in the lungs at the end of a maximal inspiration.
FRC	Functional residual capacity.	Liters	Volume of gas remaining in the lungs at the resting expiratory level.
	Alveolar volume	Liters	Volume of gas contained in pulmonary alveoli.

SOURCE: Comroe, J. et al. (*56*)

TABLE A6.—*Epidemiological studies concerning the relationship of air pollution, social class, and smoking to chronic obstructive bronchopulmonary disease (COPD)*

Author, year, country, reference	Number and type of population	Results
Higgins, 1957, England (*115*).	301 males and 280 females living in 2 separate districts. (45–64 years of age.)	Male data only (170): (a) The frequency of recurrent chest illnesses was higher in the more polluted region but the prevalence of other respiratory symptoms and mean values were similar. (b) Significant difference observed in COPD mortality rate.
College of General Practitioners, 1961, England (*55*).	787 males and 782 females 45–64 years of age from medical doctors' case lists.	(a) Male urban inhabitants manifested almost twice the prevalence of chronic bronchitis as rural males; this difference could not be explained on the basis of smoking habits. (b) No significant urban/rural differences noted for PEFR.[1] (c) No significant urban/rural differences noted for COPD symptoms among females.
Ferris and Anderson, 1962, U.S.A. (*81*).	1,219 males and females living in 3 different areas of a New Hampshire town.	Following adjustment for differences in smoking habits, no significant differences in chronic bronchitis were observed among the 3 pollution areas.
Mork, 1962, U.S.A. (*171*).	339 male trapsport employees from London and Norway.	The excess prevalence of serious respiratory symptoms (dyspnea, wheezing) and PEFR dysfunction among London Transport employees was only partly eliminated after standardization for smoking, and the author suggests that this is due to differences in air pollution levels.
Schoettlin, 1962, U.S.A. (*204*).	2,622 males 45–75 years of age.	(a) No positive correlation found between chronic respiratory illness and city size. (b) A positive correlation was found between chronic respiratory illness and cigarette smoking (particularly duration).
Anderson et al., 1965, Canada (*8*).	778 residents of Berlin, N.H., and 918 residents of Chilliwack, Canada.	Berlin, New Hampshire, has higher SO_2 and particulate air pollution levels and the higher respiratory disease prevalence rates among its residents were not accounted for by age differences, but were accounted for after standardization for smoking habits (except that PEFR and $FEV_{1.0}$ dysfunction was more prevalent in New Hampshire, and the authors suggest that this difference reflects air pollution differences).
Holland and Reid, 1965, England (*124*).	676 male transport employees in London and rural England.	(a) London employees manifested a greater prevalence of COPD symptoms and PEFR dysfunction than did the rural employees. (b) Smoking habit differences alone were not sufficient to explain this difference in COPD manifestations. (c) Both groups manifested pulmonary dysfunction correlated with tobacco consumption.
Bates et al., 1966, Canada (*27*).	216 hospitalized veterans from various areas of Canada (all standardized for age, tobacco consumption, and occupation).	Winnipeg (cleanest of all areas in SO_2 and industrial dustfall) residents manifested decreased prevalence of chest illnesses, less severe grades of dyspnea, and less sputum volume produced when compared to residents of all other areas.

TABLE A6.—*Epidemiological studies concerning the relationship of air pollution, social class, and smoking to chronic obstructive bronchopulmonary disease (COPD) (cont.)*

Author, year, country, reference	Number and type of population	Results
Ashley, 1969, England (*12*).	Standardized mortality ratios for males (1958-63) for 53 boroughs with air pollution indexes.	Positive correlations: (a) Smoke concentration and bronchitis mortality. (b) SO_2 and smoke concentration and bronchitis mortality and social class. (c) Pollution and social class.
Holland et al., 1969, England (*122*).	10,971 children over 11 years of age in 4 areas.	Factors affecting prevalence of respiratory symptoms: (a) Smoking—highly significant association. (b) Area of residence (pollution)—significant association except for periods of cough and phlegm lasting more than 3 weeks. (c) Social class, age, sex—no association noted.
Winkelstein and Kantor, 1969, U.S.A. (*235*).	842 females over 25 years of age in various regions of Buffalo.	(a) The increased prevalence of respiratory symptoms could not be explained by social class differences. (b) No overall association noted between productive cough and air pollution.
Cooley and Reid, 1970, England (*58*).	10,887 children 6-10 years of age from contrasting urban and rural areas.	Illnesses considered included chronic cough, past bronchitis, blocked nose. (a) Every geographic area showed a clear gradient of increasing illness prevalence with decreasing social class. (b) Social classes I, II, and III showed no urban/rural gradient while IV and V showed a clear excess in frequency of chest illnesses among urban residents over rural residents.
Lambert and Reid, 1970, England (*146*).	9,975 males and females responding to questionnaire survey.	(a) The trend of increasing prevalence of bronchitic symptoms from rural to urban respondents was not negated by adjustment for smoking differences. (b) After adjustment for age and smoking habits, male respondents manifested a clear correlation of persistent cough and phlegm prevalence with increasing air pollution. Correlation was not as striking in females. (c) Although the proportionate rise in symptom prevalence increased with air pollution similarly in each smoking group, the absolute differences in morbidity risk increased with increased cigarette consumption, suggesting synergistic influences of cigarette smoking and air pollution. (d) In the absence of cigarette smoking, the correlation between the prevalence of persistent cough and phlegm and air pollution was slight.

[1] See Glossary of Terms: Bronchopulmonary table A4.

TABLE A7.—*Epidemiological studies concerning the relationship of occupational exposure and smoking to chronic obstructive bronchopulmonary disease*

Author, year, country, reference	Number and type of population	Results
Higgins et al. 1956, England (*119*).	185 males (84 nonminers, 101 miners) without pneumoconiosis.	Miners showed increased symptom prevalence (breathlessness, cough, sputum). Miners showed increased prevalence of chronic bronchitis. Miners showed decreased MBC.[1] Differences in smoking between the two groups did not account for above differences.
Phillips et al., 1956, U.S.A. (*185*).	1,274 males factory employees (coke and electrolytic process).	None of the industrial environments were associated with an increased prevalence of chronic cough. Cigarette smoking and age were directly correlated with increased prevalence of chronic cough.
Higgins et al., 1959, England (*116*).	325 males 25–34 years of age and 401 males 55–64 years of age in various occupations.	Miners as compared to workers in non-dusty occupations: 25–34 years of age—significantly increased prevalence of chronic bronchitis and MBC abnormalities. 55–64 years of age—less significantly increased prevalence of chronic bronchitis and MBC abnormalities than in 25–34 years of age group. No smoking information available.
Chivers, 1959, England (*52*).	463 males in non-dusty and dusty occupations (lime and soda ash exposure).	No significant differences in PEFR[1] between dusty and non-dusty groups. Cigarette smoking (especially in those >40 years of age) was associated with decreased PEFR values.
Higgins and Cochrane, 1961, England (*115*).	300 male miners and 300 male nonminers 35–64 years of age.	Miners showed increased prevalence of symptoms and decreased MBC values which remained even after standardization for smoking habits. Total dust exposure was not directly correlated with these findings. Wives of miners showed similar symptom and test changes as compared with wives of nonminers.
Brinkman and Coates, 1962, U.S.A. (*42*).	1,317 males 40–65 years of age with various silica exposure histories.	Increased silica exposure was associated with an increased prevalence of chronic bronchitis. Highest prevalence of chronic bronchitis was noted in the non-exposed group; and this group was noted to have the highest number of smokers and highest consumption.
Hyatt et al., 1964, U.S.A. (*118*).	267 male miners and ex-miners 45–55 years of age.	Increased history of underground work was associated with an increased bronchopulmonary symptom prevalence and decreased pulmonary function values. The impairment of pulmonary function associated with underground work was separate from effect of smoking; but smoking and underground work did show additive effects.
Elwood et al., 1965, Ireland (*77*).	2,528 male and female flax workers over 35 years of age.	Preparing room workers who manifested byssinosis symptoms also showed an increased prevalence of chronic bronchitis independent of age or smoking when compared with non-preparing room workers. Female workers manifested a significant association between byssinosis symptoms and smoking while male workers did not.
Sluis-Cremer et al., 1967, South Africa (*209*).	827 miners and nonminers over 35 years of age.	Those smokers exposed to gold mine dust manifested more symptoms of COPD[1] than did non-dust exposed smokers, while prevalence of symptoms, among nonsmokers, was similar for the two groups.

TABLE A7.—*Epidemiological studies concerning the relationship of occupational exposure and smoking to chronic obstructive bronchopulmonary disease (cont.)*

Author, year, country, reference	Number and type of population	Results
Sluis-Cremer et al., 1967, South Africa (*209*). (*cont.*)	827 miners and nonminers over 35 years of age.	The dose relationship of cigarettes and COPD [1] symptoms was much more noticeable among those exposed to dust. The authors stressed the synergistic actions of cigarette smoking and dust exposure.
Bouhuys et al., 1969, U.S.A. (*39*).	455 male cotton textile workers (214 exposed to dust in carding and spinning rooms, 241 not exposed).	Those exposed to dust manifested a significantly greater prevalence of byssinosis symptoms than nonexposed. Smokers manifested a significantly greater prevalence of byssinosis symptoms than nonsmokers. No significant differences in Monday morning FEV^1 values were observed between smokers and nonsmokers. Prevalence of byssinosis symptoms did not show any relationship to length of employment.
Bouhuys et al., 1969, U.S.A. (*38*).	216 male hemp workers and 247 workers in other industries in same region, 20–69 years of age.	Hemp workers (especially the older ones) were noted to have different smoking habits from control group—fewer heavy smokers, more light smokers, more ex-smokers due to doctor's orders. Aged 20–49 — a. No difference in $FEV_{1.0}$ [1] values between controls and hemp workers in any smoking category. b. No difference in $FEV_{1.0}$ values between men in different smoking categories. Aged 50–69 — a. Hemp workers manifested decreased $FEV_{1.0}$ values in all smoking groups except for heaviest smokers. Ex-smokers had lowest $FEV_{1.0}$ values. b. Those smoking most had lower $FEV_{1.0}$ values as compared with light and nonsmokers. The authors conclude that: There appears to be no synergism between smoking and hemp exposure as to effect on $FEV_{1.0}$ although the selection process whereby those with symptoms have a greater tendency to stop smoking may obscure such a relationship.
Chester et al., 1969, U.S.A. (*49*).	139 male chlorine plant workers (55 with history of severe exposure).	Chlorine-exposed group manifested no difference in symptoms and a decreased MBC value when compared with non-exposed group. Smokers in chlorine-exposed group had significantly decreased MBC and FEV values as compared with nonsmokers in non-exposed group.
Greenberg et al., 1970, England (*97*).	121 workers in washing powder factory (48 found to be sensitized to product, 73 not).	Sensitized group manifested lower $FEV_{1.0}/FVC$ [1] values as compared with nonsensitized group even after smoking habits were controlled for.
Tokuhata et al., 1970, U.S.A. (*218*).	801 male miners	Increased mine exposure was associated with residual volume and FEV abnormalities even after adjustments for age and smoking. A systematic exposure-impairment relationship was noted only among smokers while relatively few nonsmokers showed COPD impairment. Smoking miners manifested more X-ray alterations and COPD symptoms than nonsmokers, regardless of number of years of underground exposure.

[1] See Glossary of Terms in Bronchopulmonary table A4.

TABLE A10.—*Experiments concerning the effect of the chronic inhalation of NO_2 upon the tracheobronchial tree and pulmonary parenchyma of animals*

Author, year, country, reference	Animal	Results
Freeman and Haydon, 1964 U.S.A. (*90*).	Sprague-Dawley rats.	25 p.p.m.: (a) after 37–41 days—moderate hypertrophy and hyperplasia of bronchial and bronchiolar epithelium. (b) after 146–157 days—(1) Advanced hypertrophy and hyperplasia of bronchial and bronchiolar epithelium. (2) Increased lung volume. (3) Proliferation of connective tissue.
Haydon et al., 1965 U.S.A. (*107*).	Sprague-Dawley rats.	12.5 p.p.m. to death: (a) Hypertrophy and occasional metaplasia of bronchial and bronchiolar epithelium. (b) Increase in number of actively secreting goblet cells.
Haydon et al., 1967 U.S.A. (*105*).	Albino rabbits.	8–12 p.p.m. for 4 months: (a) Abnormal dilatation of peripheral air spaces. (b) Decreased density of alveolar walls. (c) Hypertrophy and hyperplasia of bronchial epithelium (especially terminal bronchiolar). (d) Increase in size of alveolar ducts. (e) Increased elastic tissue staining. (f) Increased alveolar size.
Freeman et al., 1968, U.S.A. (*91*).	Sprague-Dawley rats.	0.8 p.p.m.–2 p.p.m. for entire lifespan: (a) Alveolar distention. (b) Reduction in number of cilia. (c) Epithelial inactivity ("dormancy").
Freeman et al., 1968, U.S.A. (*89*).	Sprague-Dawley rats.	18 p.p.m. (a) 5 days—terminal bronchiolar epithelial hypertrophy. (b) 4 weeks—(1) Widespread bronchiolar epithelial hypertrophy. (2) Non-necrotizing emphysema.
Blair et al., 1969, U.S.A. (*52*).	Female Swiss Albino mice.	0.5 p.p.m.: (a) 6 hours/day for 3 months—pneumonitis. (b) 24 hours/day for 3 months—(1) Respiratory bronchiolar obstruction. (2) Alveolar expansion and bronchiolar inflammation consistent with early focal emphysema.
Kleinerman, 1970, U.S.A. (*136*).	Male Syrian Golden hamsters.	100 p.p.m. for 5½ hours: (a) thymidine autoradiography—intense burst of proliferation of epithelium returning to normal in 4 days (more persistent distally). (b) electron microscope—(1) Decreased number of secretory cells + secretory granules. (2) Increased number of lysosomal structures. (3) No change in number of ciliated cells.

TABLE A13.—*Experiments concerning the effect of cigarette smoke or its constituents upon ciliary function*

Author, year, country, reference	System	Method [1]	Results
Mendenhall and Shreeve, 1937, U.S.A. (*164*).	*In vitro:* Calf trachea.	Cigarette smoke by direct application or in solution.	Controls—ciliary activity depressed approximately 4 percent. Experimental—ciliary activity depressed approximately 40 percent.
Rakieten et al., 1942, U.S.A. (*188*).	*In vitro:* (a) rabbit and rat tracheal rings. (b) human nasal mucous membrane	I. Nicotine in Locke-Ringers solution. II. Cigarette smoke in solution.	I. Ciliary activity depressed only upon exposure to 100 mg. percent solution. II. Ciliary activity depressed after 15–20 minutes exposure depending on concentration of smoke in solution.
Kordik et al., 1952, England (*137*).	*In vitro:* Rabbit trachea	Nicotine in Locke's solution.	Nicotine at 10^{-3} g./cc had no effect on ciliary activity.
Hilding, 1956, U.S.A. (*120*).	*In vitro:* Cow trachea	Cigarette smoke (direct exposure).	All tracheas showed depressed or absent ciliary activity.
Krueger and Smith, 1958, U.S.A. (*139*).	*In vivo:* Rabbit trachea	Cigarette smoke.	Cigarette smoke decreased ciliary activity by approximately 200 beats/minute.
Dalhamn, 1959, Sweden (*59*).	*In vivo:* I. Rat trachea *In vitro:* II. Rabbit trachea III. Human ciliated mucosa	Cigarette smoke.	I. 7/10 showed cessation of ciliary activity after one exposure. II. 6/10 showed cessation of ciliary activity after one exposure. III. 6/7 showed cessation of ciliary activity after one cigarette exposure.
Falk et al., 1959 U.S.A. (*80*).	*In vitro:* Rat and rabbit tracheal epithelium.	Cigarette smoke.	Decreased ciliary activity noted on exposure to cigarette smoke: (a) Repetitive exposure was associated with persistence of response over longer periods of time. (b) "Tar"-rich cigarette was more inhibitory than "tar"-poor. (c) Filtered smoke was less inhibitory than unfiltered.
Ballenger, 1960, U.S.A. (*25*).	*In vitro:* Human bronchial and tracheal epithelium obtained during anesthesia.	Cigarette smoke in solution.	Ciliary activity was fully inhibited within 6–28 minutes of exposure depending upon concentration of smoke in solution.

TABLE A13.—*Experiments concerning the effect of cigarette smoke or its constituents upon ciliary function (cont.)*

Author, year, country, reference	System	Method [1]	Results
Wynder et al., 1963, U.S.A. (*256*).	*In vivo:* Fresh water mussel ciliated epithelium.	Cigarette smoke; and its fractions in solution.	Unfiltered cigarette smoke—ciliastasis by 2nd-5th puff. Acid (phenolic) fraction solution—immediate ciliastasis. Whole extract fraction solution—no ciliastasis. Neutral fraction solution—no ciliastasis. 1 percent phenol solution—immediate ciliastasis.
Dalhamn and Rylander, 1964, Sweden (*61*).	*In vivo:* Cat trachea.	Cigarette smoke.	Unfiltered cigarettes—ciliastasis in 3/5 cats after 5 cigarettes. Filtered cigarettes—no ciliastasis after 8 cigarettes (5 cats). Controls—no ciliastasis (5 cats).
Ballenger et al., 1965, U.S.A. (*25*).	*In vitro:* Human ciliated tracheal epithelium obtained during anesthesia.	Nicotine in solution.	Initial stimulation of activity followed by decline and complete ciliastasis after 12–24 hours of exposure.
Dalhamn and Rylander, 1965, Sweden (*62*).	*In vivo:* Cat trachea.	Cigarette smoke.	The longer the time interval between exposures, the more puffs were required to cause ciliastasis.
Wynder et al., 1965, U.S.A. (*255*).	*In vivo:* Fresh water mussel ciliated epithelium	Various compounds in solution.	Formic, acetic, propionic, benzoic acids all more ciliatoxic than phenol. Oxalic acid less ciliatoxic than phenol. Formaldehyde, acrolein more ciliatoxic than phenol.
Carson et al., 1966, U.S.A. (*44*).	*In vivo:* Cat trachea.	Cigarette smoke.	*Percent decrease in ciliary activity* Control ..... 0 Unfiltered smoke ..... 53 Cellulose acetate filter ..... 45 Carbon cellulose acetate filter 30
Dalhamn, 1966, Sweden (*60*).	*In vivo:* Cat trachea.	Cigarette smoke.	*Mean number of puffs required to produce ciliastisis* No filter ..... 91 Charcoal filter ..... 170 Commercial cellulose acetate filter ..... 194 Charcoal and acetate filter ..... 512 Cambridge filter 600
Kensler and Battista, 1966, U.S.A. (*155*).	*In vivo:* Rabbit trachea, cat trachea, dog trachea, monkey trachea, rat trachea.	Cigarette smoke and components in Tyrode's solution.	Rabbit trachea—Total smoke condensate of 3 cigarettes, gas phase condensate of 7 cigarettes caused similar ciliastasis. Other species—All found sensitive to ciliastatic components of cigarette smoke. Bulk of activity noted in gas phase (HCH, formaldehyde, acrolein).

TABLE A13.—*Experiments concerning the effect of cigarette smoke or its constituents upon ciliary function (cont.)*

Author, year, country, reference	System	Method [1]	Results
Dalhamn and Rylander, 1967, Sweden (*63*).	*In vivo:* Cat trachea.	Cellulose acetate-filter cigarettes with varying amounts of "tar" but similar gas phases.	Increased amounts of tar were associated with decreased number of puffs required to inhibit ciliary activity.
Dalhamn and Rylander, 1968, Sweden (*64*).	*In vivo:* Cat trachea.	Unfiltered and Cambridge-filter cigarettes.	Whole smoke found to be markedly more toxic to ciliary activity than volatile (gas) phase at lower dosages (puff volume). This difference diminishes with increasing puff volume.
Kaminski et al., 1968, U.S.A. (*153*).	*In vivo:* Cat trachea.	Whole and filtered cigarette smoke exposed or unexposed to "wet chamber" made to stimulate oral mucosa and saliva.	Wet chamber adsorption significantly reduced the ciliastatic activity of whole smoke, but did not affect the ciliastatic activity of smoke previously filtered by Cambridge or charcoal filters.
Krahl and Bulmash, 1969, U.S.A. (*158*).	*In vivo:* Common mollusk ciliated epithelium.	Cigarette smoke dissolved in sea water.	Significant ciliastasis, reversible.
Battista and Kensler, 1970, U.S.A. (*25*).	*In vitro:* Chicken tracheal epithelium.	Cigarette smoke or HCN in Tyrode's solution.	The authors observed that: (1) The more diluted smoke required more puffs to cause ciliastasis. (2) Activated charcoal filtered smoke was less ciliastatic than cellulose acetate filtered smoke and also contained less HCN and acrolein. (3) HCN alone was ciliastatic but recovery was more rapid than after cigarette smoke alone. They conclude that the gas phase components are more related to ciliastasis (as particulate matter is not significantly decreased by charcoal filtration while HCN and acrolein are).
Battista and Kensler, 1970, U.S.A. (*29*).	*In vivo:* Hen trachea.	Cigarette smoke.	The authors observed that: (1) Whole smoke acutely depressed ciliary activity in 4–6 puffs. (2) Gas phase was only slightly less depressant than whole smoke. (3) Chronic exposure (1 cigarette/day for 32 days) to smoke resulted in no apparent permanent defect in ciliary activity (although mucous production was significantly increased).

TABLE A13.—*Experiments concerning the effect of cigarette smoke or its constituents upon ciliary function (cont.)*

Author, year, country, reference	System	Method [1]	Results
Dalhamn and Rylander, 1970, Sweden (65).	*In vivo:* Cat trachea.	Unfiltered cigarette and cigar smoke.	*Average number of puffs required to arrest ciliary activity* Cigarette smoke ..... 73 Cigar smoke .....114 } ($p<0.01$) The authors note that cigar smoke is of a different pH and that it contains more isoprene, acetone, toluene, and acetonitrile.
Kennedy and Elliott, 1970, U.S.A. (134).	*In vivo:* Protozoan (ciliated).	Mainstream cigarette smoke.	Electron microscopic observations: (1) After 7 minutes exposure—alteration of mitochondrial structure. (2) After 42 minutes exposure—destruction of internal mitochondrial membrane structure. (3) Gas phase alone, while ciliatoxic, did cause mitochondrial swelling but no disruption of membrane structure.

[1] *Unless otherwise stated, method entailed the direct observation of ciliary activity using markers.*

TABLE A14.—*Experiments concerning the effect of cigarette smoke on pulmonary surfactant and surface tension*

Author, year, country, reference	System	Method	Results
Miller and Bondurant, 1962, U.S.A. (*165*)	Rat lung extracts	Cigarette smoke: (1) Applied to extract. (2) Exposure of rats.	(1) Exposure to cigarette smoke was associated with decreased surface tension in lung extract. (2) Surface tension of rats (lung extracts) exposed to cigarette smoke was decreased as compared with those not exposed.
Cook and Webb 1966, U.S.A. (*57*)	40 subjects undergoing bronchoscopy: 14 *normal* 7 nonsmokers with pulmonary disease 19 *smokers* with and without pulmonary disease.		*Surface tension values of surfactant*: *20 percent area*; *100 percent area*; *Stability index (reflects surfactant activity)*. Normal: 6.5; 60.0; 1.61. Pulmonary patients: †17.0; †50.0; 1.00. Chronic smokers: 15.7; 51.0; 1.04. † Values significantly different from values of normals at $p<0.02$ level.
Glammona 1967, U.S.A. (*94*)	*In vitro:* Surfactant material induced from dogs and rats. *In vivo:* Dogs, cats, and guinea pigs.	Exposed to cigarette smoke for 3 hours/day for up to 3 weeks.	*In vitro:* Exposure to cigarette smoke was associated with a significant decrease in maximal surface tension. *In vivo:* Dogs and cats (exposed for 1 week)—no significant change. Guinea pigs (exposed for 3 weeks)—significant decrease in maximal surface tension.
Webb, et al. 1967, U.S.A. (*224*)	Bronchial washing, from dog lungs.	Direct exposure to cigarette smoke.	*Surface tension values of surfactant*: *20 percent area*; *100 percent area*. Control: Number 11; 7.1; 60.7. Smoke: Number 10; 18.7; 45.8. ($p<0.002$ for both). *Stability index*: 1.60; 0.84.

TABLE A16.—*Studies concerning the relationship of smoking to infectious respiratory disease in humans*

(Actual number of cases shown in parentheses)

SM = Smokers NS = Nonsmokers

Author, year, country, reference	Number and type of population	Data collection	Results					Comments
Mills, 1950, U.S.A. (*167*).	118 male and female patients with pneumonia and 472 healthy individuals from "random" sample.	Hospital Interview.		*Cases*	*Controls*			The author stated that there was a significant difference in tobacco usage between the two groups.
			Mean age	49.6	49.6			
			NS	15.25	25.21			
			Cigarettes only	63.56	52.33			
			Mixed	21.19	22.46			
Lowe, 1956, England (*157*).	520 male and 185 female tuberculosis patients and 419 male and 249 female control outpatients.	Interview by trained social worker.		*Males*		*Females*		Cigarette smokers include pipe smokers. The author noted a significant deficiency of non- and light smokers and an excess of heavy smokers among the cases
				Cases	*Controls*	*Cases*	*Controls*	
			NS	2.5	8.1	37.3	51.4	
			Cigarettes/day: 1–9	9.2	12.9	20.5	25.7	
			10–19	38.1	35.6	30.8	20.5	
			20–29	29.4	27.4	11.4	2.4	
			30–39	11.3	9.3			
			>40	9.4	6.7			
Dowling, et al., 1957, U.S.A. (*71*).	Individuals exposed to "infectious cold agent" and placebo.	Interview and medical examination.		*Exposed to placebo*		*Exposed to infectious agent*		No statistically significant differences noted.
				Number	*Percent developing "cold"*	*Number*	*Percent developing "cold"*	
			NS	111	10	328	34	
			SM	78	14	249	36	

TABLE A15.—*Studies concerning the relationship of smoking to infectious respiratory disease in humans (cont.)*

(Actual number of cases shown in parentheses)
SM = Smokers NS = Nonsmokers

Author, year, country, reference	Number and type of population	Data collection	Results				Comments
Boake, 1958, U.S.A. (*33*).	Parents of 59 families.	Interview		*Person-years*	*Number of respiratory illnesses*	*Illnesses/ person-years*	No statistically significant differences noted.
			NS .....(24)	120	624	5.2	
			Cigarettes/day: 1–10 .....(19)	99	529	5.3	
			11–20 .....(25)	108	486	4.5	
			>20 .....(19)	99	424	4.3	
			Pipe, cigar .....(14)	72	304	4.2	
Shah et al., 1959, India (*205*).	Tuberculosis institute employees.	Survey, X-ray, and interview.		*Tuberculous by X-ray*	*Normal or nontuberculous*		† Numbers in parentheses represent figures "expected" by use of 2 x 2 contingency table.
			NS	†10 (19.7)	178 (168.3)		
			SM	36 (26.3)	215 (224.7)		
							Tuberculous employees were found to have significantly fewer nonsmokers and more smokers.

TABLE A15.—*Studies concerning the relationship of smoking to infectious respiratory disease in humans (cont.)*

(Actual number of cases shown in parentheses)
SM = Smokers NS = Nonsmokers

Author, year, country, reference	Number and type of population	Data collection	Results	Comments
Brown et al., 1961, Australia (*4*).	306 male and female tuberculosis clinic patients, 221 male and female outpatients.	Interview	*Smoking habits prior to diagnosis* *Tuberculous patients (percent)* / *Controls (percent)* NS ..... 9.1 / 19.0 Cigarettes/day: 1–9 ..... 10.5 / 15.4 10–19 ..... 34.3 / 19.5 20–29 ..... 26.3 / 25.8 30–39 ..... 7.2 / 5.4 >40 ..... 6.2 / 9.1 Pipes ..... 5.9 / 4.6	Data presented only on Queensland sample. The authors noted that the significant difference between the patients and controls was not present when the groups were matched for alcohol intake.
Haynes et al., 1966, U.S.A. (*108*).	191 male prep school students.	Interview	*Average number of respiratory illnesses/10 students (adjusted for age)* *All respiratory episodes* / *All severe respiratory episodes* / *All severe lower or combined respiratory episodes* NS (99) ..... 11.1 / 1.6 / 0.36 SM (92) ..... 20.2 / 6.7 / 3.34	
Parnell et al., 1966 Canada (*181*).	47 smoking-nonsmoker pairs of student nurses matched for age and parents' occupational class.	Interview and health service records.	*Median number of illnesses/student* *All respiratory diseases*† / *All other illnesses* NS (47) ..... 2.08 / 2.99 SM (47) ..... 2.64 / 5.00	The authors noted that these differences were statistically significant. † Particularly tracheitis, bronchitis, and pneumonia.

TABLE A15.—*Studies concerning the relationship of smoking to infectious respiratory disease in humans (cont.)*

(Actual number of cases shown in parentheses)

SM = Smokers NS = Nonsmokers

Author, year, country, reference	Number and type of population	Data collection	Results	Comments
Peters et al., 1967, U.S.A. (*183*).	1,496 Harvard and 370 Radcliffe students.	Medical history, chart review, and questionnaire.	*Number of visits to student health unit for respiratory illness/student (common colds, pharyngitis, bronchitis, laryngitis, pneumonia—not allergic rhinitis)* *Harvard* / *Radcliffe* NS ..... 1.44 (771) / 1.44 (193) SM ..... †2.27 (726) / 2.27 (177) <2 years smoked ..... 2.00 3–4 ..... 2.30 >5 ..... 2.50	† $p<0.001$.
Finklea et al., 1969 U.S.A. (*89*).	1,811 male college students.	Questionnaire prior to A_2/HK/68 epidemic and follow-up on morbidity.	Heavy smokers—21 percent more clinical illnesses than nonsmokers; 20 percent more requiring bed rest than nonsmokers Light smokers—10 percent more clinical illnesses than nonsmokers; 7 percent more requiring bed rest than nonsmokers	The authors also noted that: (a) Smokers exhibited serologic evidence of increased subclinical A_2/HK/68 infection. (b) There was no difference in the vaccination status between smokers and nonsmokers.

TABLE A16.—*Complications developing in the postoperative period in patients undergoing abdominal operations*

Group	Cases	Percent chest clear	Percent bronchitis	Percent broncho-pneumonia and atelectasis	Percent total complication rate
Men over 20					
Smokers	300	41.7	53.0	5.3	58.3
Light Smokers	180	68.4	27.7	3.9	31.6
Nonsmokers	66	92.5	6.0	1.5	7.5
Women over 20					
Smokers	23	39.1	43.5	17.4	60.9
Light Smokers	62	77.5	20.9	1.6	22.5
Nonsmokers	518	88.8	8.1	3.1	11.2

SOURCE: Morton, H. J. V. (*173*)

TABLE A17.—*Arterial oxygen saturation before and after operation*

Group	Case number	Arterial oxygen saturation (percentage) Before operation	Day 1	Day 2	Day 3
Nonsmokers	1	94	93	94	..
	2	94	93	94	..
	3	96	93	94	..
	4	95	90	94	..
	5	94	90	93	..
Smokers	6	95	91	89	91
	7	92	89	81	89
	8	91	89	85	89
	9	93	91	88	92
	10	90	87	88	92

SOURCE: Morton, A. (*172*).

Chapter 4

Cancer

Source: 1971 Report, Chapter 4, pages 231 - 384.

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INTRODUCTION

During the early years of this century, a number of pathologists and clinicians reported a dramatic increase in the incidence of lung cancer. Autopsy studies and studies of lung cancer death rates revealed a significant increase beginning prior to World War I and continuing during the ensuing years. This epidemic of lung cancer continues to the present day, with nearly 60,000 deaths expected from this disease in the United States during 1970.

Beginning in the 1920's, a number of reports appeared which suggested a relationship between lung cancer and tobacco smoking (*4, 203, 278*). Since that time, many clinical and epidemiological studies have been published which confirm this relationship. The 1964 Report (*291*) contains a thorough review and analysis of the data available at that time as well as an excellent discussion of the considerations necessary for their evaluation.

Major epidemiological studies have demonstrated that smokers have greatly increased risks of dying from lung cancer compared to nonsmokers. An increased risk of lung cancer has been found for every type of smoking habit investigated, but two characteristics of the risk are particularly evident: The risk is much greater for cigarette smokers than for smokers of pipes and cigars, and among cigarette smokers a dose relationship exists. That is, the more one smokes, as measured by total pack-years of smoking, present level of smoking, degree of inhalation, or age at start of smoking, the greater is the risk. It has also been shown that the risk of lung cancer among ex-smokers decreases with time almost to the level of nonsmokers; the time required is dependent on the degree of exposure prior to cessation.

Pathologists have found that the squamous cell or epidermoid form of lung cancer is the most prevalent one in cigarette smoking populations and that this form accounts for a major portion of the rise in lung cancer deaths (*154*). Such studies have also indicated a lower prevalence among smokers for oat-cell and adenocarcinomas of the lung than for the squamous form, but in most studies a higher frequency of these tumors is found among smokers than among nonsmokers.

Smoking has been implicated in the development of other types of cancer in humans. Among these is cancer of the larynx. A num-

ber of epidemiological studies have demonstrated increased mortality rates for laryngeal cancer in smokers, particularly cigarette smokers, compared with nonsmokers. Autopsy studies have revealed that a clear dose-relationship exists between smoking and the development of cellular changes in the larynx, including carcinoma *in situ*.

Cancers of the mouth and oropharynx have been found to be more common among users of all types of tobacco than among abstainers. Although smoking is a definite risk factor in the development of malignant lesions of the oral cavity and pharynx, its relative contribution in conjunction with other factors such as poor nutrition and alcohol consumption has not been fully clarified.

Similarly, although smokers are more likely to develop carcinoma of the esophagus than nonsmokers, the relative additional contribution of smoking in conjunction with nutritional factors and alcohol consumption requires clarification.

Smokers have been found to be more at risk for the development of cancer of the urinary bladder than are nonsmokers, and there is evidence to suggest that some smoking-induced abnormal metabolic product or abnormal concentration of a metabolic product may be responsible for this increased risk. In addition, cancer of the kidney is apparently more common in smokers than in nonsmokers, but the epidemiologic evidence for this relationship is not as definite as for bladder cancer.

Epidemiological studies have indicated an association between smoking and cancer of the pancreas. The significance of this relationship is unclear at this time.

Experimental studies have demonstrated the carcinogenicity of the condensate of tobacco smoke, or "tar." This material, when painted on the skin of animals, leads to the development of squamous cell tumors of the skin. Researchers have shown that this condensate contains substances known as carcinogens, capable of inducing cancers. Among these carcinogens are several chemicals which have been identified as tumor initiators, that is, compounds which initiate changes in target cells and also tumor promoters, or compounds which promote the neoplastic development of initiated cells. Other, as yet unidentified, factors are presumably also involved because the sum of the carcinogenic effects of the known agents does not equal that of cigarette smoke condensate.

Numerous experiments have been performed in which whole cigarette smoke, filtered smoke, or certain constituents of smoke, such as the "tar," are administered by varying methods to animals or to tissue and cell cultures in order to investigate the neoplastic-inducing properties of cigarette smoke. Particular difficulty has been encountered in experiments which have attempted to deliver

whole cigarette smoke to the larynx and into the lungs of experimental animals. This has resulted in the use of other methods such as the implanting of pellets containing suspected carcinogens and the instilling into the trachea of suspected carcinogens as such, or adsorbed onto fine inert particulate matter as a carrier. The difficulty with the inhalation studies has been twofold. First, the animals, particularly the smaller species such as the rat, frequently die from the acute toxic effects of the nicotine and carbon monoxide in the tobacco smoke. Second, the upper respiratory tract of experimental animals, particularly the nose, is much different from analogous human structures, resulting in a more efficient filtration of smoke in the upper respiratory tract. Nevertheless, in rodents and canines, progressive changes apparently indicative of ultimate neoplastic transformation have been identified in the respiratory tract.

Recently, two studies in different species and in different target organs have been reported concerning the development of early invasive cancer following the prolonged inhalation of cigarette smoke. Auerbach and his coworkers (*11*) trained dogs to inhale cigarette smoke through a tracheostoma. After approximately 29 months of daily exposure, these investigators found a number of cancers of the lung.

Dontenwill (*76*) in the second of these two studies, exposed hamsters to the passive inhalation of cigarette smoke over varying and prolonged periods of time. He observed the development of premalignant changes and, ultimately, invasive squamous cell cancer of the larynx.

LUNG CANCER

Cancer of the lung in the United States accounted for 45,383 deaths among males and 9,024 deaths among females in 1967 (*289*). It is presently estimated that approximately 60,000 people will die of lung cancer during 1970.

The alarming epidemic of lung cancer is a relatively recent phenomenon. Death rates for lung cancer (ICD Codes 162, 163) rose from 5.6 (per 100,000 resident population per year) in 1939 to 27.5 in 1967 (*289*, *290*). This rapid increase followed the increased use of cigarettes among the United States population. The increase has occurred principally among males, although more recently females have shown a similar rising pattern.

The converging evidence for the conclusion that cigarette smoking is the major cause of lung cancer is derived from varied types of research including epidemiological, pathological, and laboratory investigations.

EPIDEMIOLOGICAL STUDIES

Numerous epidemiological studies, both retrospective and prospective, have been carried out in different parts of the world to investigate the relationship between smoking and cancer of the lung. These studies are outlined in tables 1, 2, A3, and A4.

Prospective Studies

The major prospective studies concerning the relationship of smoking and lung cancer are presented in table 1. In all, these investigations have studied more than a million persons from a number of different populations for up to 10 years. These studies show increased lung cancer mortality ratios for cigarette smokers of all amounts ranging from 7.61 to 14.20 among male smokers as compared to nonsmoking males. The one major prospective study of female cigarette smokers reveals an overall mortality ratio of 2.20 (*118*).

Also uniformly present in these studies is a dose-related increase in the mortality from lung cancer with increasing amounts of cigarettes smoked per day. Other measures of exposure show similar trends. Hammond (*118*) reported increased mortality ratios associated with increased inhalation (table 1) as well as with increased duration of smoking (table 2).

Ex-smokers show significantly lower lung cancer death rates than continuing smokers. In their study of more than 40,000 British physicians, Doll and Hill (*74, 75*) noted a decrease in lung cancer mortality rates with increasing time since smoking stopped (table 1). During the past 20 years, half of all the physicians in Britain who used to smoke cigarettes have stopped smoking. While the death rates from lung cancer rose by 7 percent among all men from England and Wales during the period from 1953–57 through 1961–65, the rates for male doctors of the same ages fell by 38 percent (*96*).

Pipe and cigar smokers have been shown in the prospective studies to have lung cancer mortality rates higher than those of nonsmokers, although these are generally substantially lower than those of cigarette smokers (table 1).

Retrospective Studies

More than 30 retrospective (case-control) studies have been reported concerning the relationship of smoking and lung cancer. These studies are outlined in tables A3 and A4. Table A4 presents the percent of nonsmokers and of heavy smokers among both cases and controls as well as the relative risk ratios for all smokers.

TABLE 1.—*Lung cancer 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	collection Data	Follow-up years	Number of deaths	Regular cigarette smoking only (cigarettes/day)	Pipe cigar	Inhalation	Exsmokers	Comments
Hammond and Horn, 1958, U.S.A. (*120*).	187,783 white males in 9 States ages 50–69.	Questionnaire and interview.	3½	448 SM . 443 NS . 15	NS ..... 1.00 (15) <10 .... 8.00 (24) 10–20 ...10.50 (84) >20 ....23.40(117) All ....†10.73(397)	*Pipe* NS ... 1.00 (15) SM ... 2.07 (18) *Cigar* NS ... 1.00 (15) SM ... 1.00 (7)	No data	*Bronchogenic* *(Excluding adenocarcinoma)* Never smoked ..... 1.00 *Previously <1 pack/day* Continuing .....16.94 Duration of cessation: <1 year ..16.60; 1–10 years .10.44; >10 years .. 1.51 *Previously >1 pack/day* Continuing .....46.21 Duration of cessation: <1 year ..58.23; 1–10 years .22.82; >10 years ..17.79	341/448 deaths with microscopic proof. Includes those regular cigarette smokers who also smoked pipes and cigars. † With or without microscopic proof.
Doll and Hill, 1964, Great Britain (*74*).	Approximately 41,000 male British physicians	Questionnaire and followup of death certificate.	10	212 SM . 209 NS . 8	NS ..... 1.00 (3) 1–14 .... 8.14 (22) 15–24 ...19.86 (53) >25 ....32.43 (57)	*Pipe and Cigar* NS .... 1.00 (3) *Grams/day* 1–14.. 6.00 (12) 15–24.. 6.43 (6) >25 ...13.71 (3)	No data	*Cigarette smokers* NS ..... 1.00 (3) Continuing .....18.29(124) Duration of cessation: <5 years .. 9.57 (5); 5–9 years . 7.00 (7); 10–20 years . 2.67 (3); >20 years . 2.71 (2)	
Best, 1966, 1966, Canada (*21*).	Approximately 78,000 male Canadian veterans.	Questionnaire and followup of death certificate.	6	331 †SM . 324 NS . 7	NS ..... 1.00 (7) <10 ....10.00 (57) 10–20 ...16.41(204) >20 ....17.31 (63) All .....14.20(245)	*Pipe* NS ....1.00 (7) SM ....4.35 (18) *Cigar* NS ....1.00 (7) SM 2.94 (2)	No data	NS ..... 1.00 (7) Ex-smokers of cigarettes only 6.06 (18)	† Refers to current cigarette smokers only.

TABLE 1.—*Lung cancer mortality ratios (cont.)*

(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	Regular cigarette smoking only (cigarettes/day)	Pipe cigar	Inhalation	Exsmokers	Comments
Kahn (Dorn), 1966, U.S.A. (*118*).	U.S. male veterans 2,265,674 person years.	Questionnaire and followup of death certificate.	8½	1,256 SM .1,178 NS . 78	NS ..... 1.00 (78) 1–9 .... 5.49 (45) 10–20 ... 9.91 (303) 21–39 ...17.41 (815) >39 ....23.93 (82) All 12.14 (749)	*Pipe* NS ....1.00 (78) SM ....1.84 (17) *Cigar* NS ....1.00 (78) SM ....1.59 (6) *Pipe and cigar* NS ....1.00 (78) SM 1.66 (20)	No data	NS ..... 1.00 (78) *Number of cigarettes/day:* 1–9 ..... 0.95 (4) 10–20 ..... 8.48 (89) 21–39 ..... 9.38 (57) >39 ..... 8.24 (19)	
Hammond, 1966, U.S.A. (*118*).	440,558 males 562,671 females 35–84 years of age in 25 States.	Interviews by ACS volunteers.	4	*Males* 1,159 SM .1,110 NS . 49 *Females* 188 SM . 81 NS . 102	*Current cigarettes only* *Males* NS ..... 1.00 (49) 1–9 .... 4.60 (26) 10–19 ... 7.48 (82) 20–39 ...13.14 (381) >40 ....16.61 (82) All ..... 9.20 (719) *Females* NS ..... 1.00 (102) 1–19 .... 1.06 (20) >20 .... 4.76 (50) All 2.20 (81)	*Pipe* NS ....1.00 (49) SM ....2.24 (21) *Cigar* NS ....1.00 (49) SM ....1.85 (22) *Pipe and cigar* NS ....1.00 (49) SM 0.90 (11)	*Males* NS ..... 1.00 (49) Slight ..... 8.42 (120) Moderate ...11.45 (311) Deep .....14.31 (141) *Females* NS ..... 1.00 (102) Slight ..... 1.78 (25) Moderate, Deep .. 8.70 (45)		ICD code 162 only.

TABLE 1.—*Lung cancer mortality ratios (cont.)*

(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	Regular cigarette smoking only (cigarettes/day)	Pipe cigar	Inhalation	Exsmokers	Comments
Buell et al., 1967, U.S.A. (49).	69,868 American Legionnaires 35–75 years of age and older.	Questionnaire and followup of death certificate.	3	304	NS .... 1.00 <20 .... 2.30 20 ... 3.50 >20 .... 4.90				
Hirayama, 1967, Japan (125).	265,118 male and female adults 40 years of age and older.	Trained PHS nurse interview and followup of death certificate.	1½	43 SM . 40	NS ..... 1.00 (3) 1–24 ... 2.69 (29) >25 .... 5.68 (5)				Preliminary report.
Weir and Dunn, 1970, U.S.A. (506).	68,153 males in various occupations in California.	Questionnaire and followup of death certificate.	5–8	868	NS .... 1.00 ±10 .... 8.72 ±20 .... 9.05 >30 .... 9.56 All 7.61				NS include pipe and cigar smokers SM include ex-smokers.

[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 exsmokers.

TABLE 2.—*Lung cancer mortality ratios for males by duration of cigarette smoking*
(Actual number of deaths are shown in parentheses)

Age began cigarette smoking	35–54	55–69	70–84	35–84
25 or older	2.77 (5)	3.39 (12)	3.38 (3)	3.21 (20)
20–24	5.83 (31)	11.11 (72)	12.11 (7)	9.72(110)
15–19	8.71(112)	13.06(176)	19.37(27)	12.81(315)
<15	12.80 (36)	16.81 (57)	16.76 (9)	15.10(101)

SOURCE: Hammond,E. C. (118).

These smoker-nonsmoker risk ratios range from 1.2 to 36.0 for males and from 0.2 to 5.3 for females.

Although not presented in tabular form, the data concerning lung cancer and pipe or cigar smoking are similar to those found by the prospective studies mentioned above. However, a study by Abelin and Gsell (*1*) conducted on a rural Swiss population noted that an increased risk of lung cancer was present among heavy cigar and pipe smokers (as well as cigarette smokers) to a greater degree than previously reported. The authors suggest that their findings might be due to differences in either the amount smoked or the carcinogenicity of Swiss and German cigars. The difference might also be explained by the greater use and more frequent inhalation of small cigars in Switzerland as compared to other countries where large cigars are more commonly smoked but rarely inhaled. Kreyberg (*154*), in a review of 887 cases of lung cancer in Norway, noted that pipe smokers showed an increased risk of lung cancer, although this risk was substantially lower than that for cigarette smokers.

LUNG CANCER TRENDS IN OTHER COUNTRIES

Several studies of particular interest are those in which the changing mortality from lung cancer has been investigated in countries in which cigarette smoking has become popular and widespread only in recent years. In those countries where accurate statistics for lung cancer mortality are available for both the pre-smoking and post-smoking periods, long-term trends can be studied in some detail.

Two such studies have dealt with lung cancer mortality trends in Iceland. Dungal (*83*) noted in 1950 that lung cancer was a rare disease in Iceland and felt that this rarity could be explained by the relatively late onset of heavy tobacco smoking in the Icelandic population when compared to that of Great Britain and Finland. He observed that the annual per capita consumption of tobacco did not reach one pound in Iceland until 1945, while Great Britain and Finland passed that amount before 1920. In 1967, Thorarinsson, et al. (*276*) noted a sharp rise in the incidence of lung cancer in Ice-

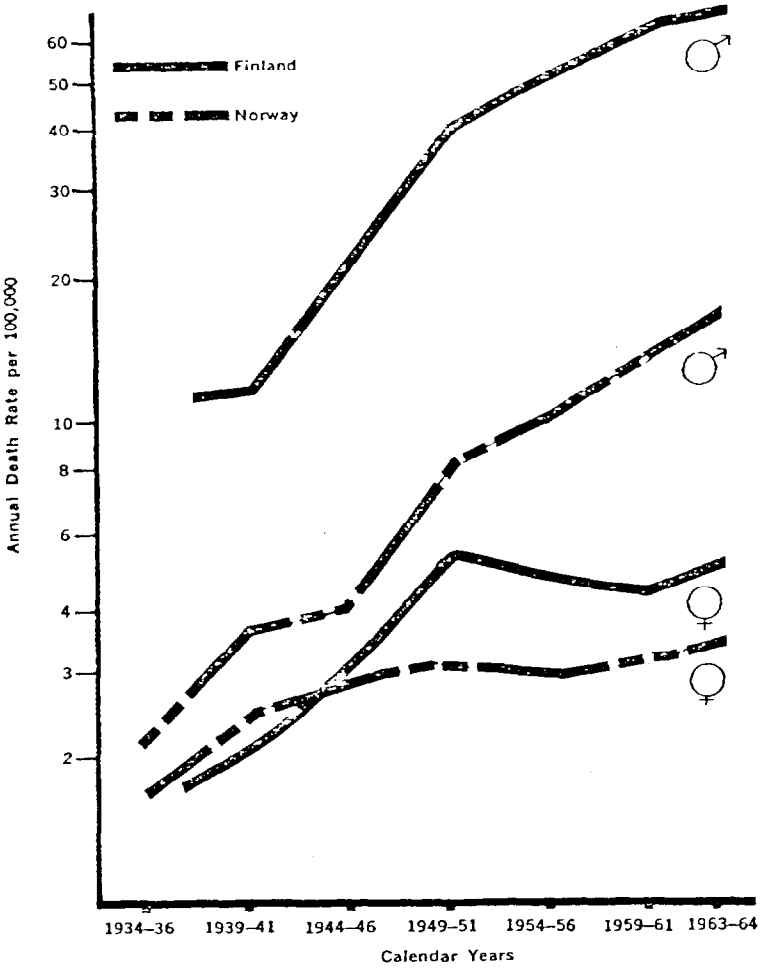

FIGURE 1.—Lung cancer, Finland and Norway.
SOURCE: Kreyberg, L. (154).

land after 1950 and found a correlation between that increase and the increasing sale of cigarettes in that country.

Kreyberg (*154*) analyzed the lung cancer death rates of both Norway and Finland in relation to the use of tobacco in those two countries over the past 100 years. Figure 1 shows the substantial difference in lung cancer mortality between the two countries. Kreyberg observed that cigarettes came into use in Norway in 1886 while the Finnish population (more closely allied to Russia socio-economically) was consuming more than 100 million cigarettes per year during the decade of the 1880's. Cigarettes remained scarce in Norway until after World War I, and this 30-year lag in consump-

TABLE 5.—*Annual means of total lung cancer mortality and sex ratios for selected periods in Finland and Norway*

Year	Finland		Norway	
	Males	*Females*	*Males*	*Females*
1936–38	192	33	34	30
Sex ratio	5.8 : 1		1.1 : 1	
1963–66	1,319	121	355	79
Sex ratio	10.9 : 1		4.5 : 1	

SOURCE: Kreyberg, L. (154).

tion behind that of Finland is reflected in a similar lag in total lung cancer mortality and sex ratios (table 5).

HISTOLOGY OF LUNG TUMORS

A number of investigators have focused their interest upon the relationship of cigarette smoking to the varied histology of lung tumors. The major histological types of lung cancer include squamous cell (epidermoid) carcinoma, small and large cell anaplastic carcinomas, adenocarcinoma (including bronchiolar and alveolar types), and undifferentiated carcinoma (*153*). A review of these studies (table 6) indicates a closer relationship between cigarette smoking and epidermoid carcinoma than between cigarette smoking and adenocarcinoma (*42, 113*).

The work of Kreyberg (*153*) in Norway, over the past 20 years, provides evidence of a specific histologic relationship. This investigator noted that a clearer association is obtained if the various types of pulmonary carcinomas are grouped. Table A7 presents his groupings of the specific histologic types. Using this classification as a basis for analysis of lung cancer sex-ratios in Norway, Kreyberg has observed that Group I carcinomas are significantly more frequent among males while Group II carcinomas show an approximately equal distribution among males and females. The author considers the recent rise in lung cancer in Norway to be a reflection of the increased prevalence of Group I carcinomas. Table 8 presents a summary of Kreyberg's investigation concerning 793 male and female cases of lung cancer. Among both males and females, the risk ratio among smokers is substantially higher for Group I types than for those of Group II. However, adenocarcinoma among males shows a risk ratio of 2.9, signifying a relationship with smoking. Kreyberg attributes the lower rates noted among females to their significantly lower consumption of tobacco in all forms.

TABLE 6.—*Epidemiologic and pathologic investigations concerning smoking and the histology of lung cancer*[1]

(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of persons and case selection method	Results			Comments
Wynder and Graham, 1950, U.S.A. (*516*).	644 autopsies on males with confirmed lung cancer.	*Percent cases by histologic type and smoking history*	*All lung cancers other than adenocarcinoma (605)*	*Adenocarcinoma (39)*	The percentage of chain smokers in the general population (7.6) was significantly less than among the patients with adenocarcinoma. The authors refrained from making any definite conclusions due to the insufficient number of cases.
		Nonsmokers	1.3	10.3	
		Light cigarette smokers	2.3	7.7	
		Moderate	10.1	15.4	
		Heavy	35.2	38.5	
		Excessive	30.9	10.3	
		Chain	20.3	18.7	
Doll and Hill, 1952, England (*73*).	916 male and 79 female cases with histologically confirmed lung cancer.	*Percent patients with lung cancer by average amount smoked daily over 10 years*			No statistically significant difference was found between the amounts smoked by the patients in the different histological groups. Number of proven adenocarcinomas too small for conclusions.
			Males		
			Epidermoid (475)	*Oat-cell or anaplastic (303)*	*Adenocarcinoma (33)*
		Nonsmokers	0.2 (1)	0.7 (2)	6.1 (2)
		Smokers:			
		<5 cigarettes/day	2.9 (14)	3.9 (12)	6.1 (2)
		5–14	35.6 (169)	36.3 (110)	21.2 (7)
		15–25	36.8 (175)	34.7 (105)	48.5 (16)
		>25	24.4 (116)	24.4 (74)	18.2 (6)
			Females		
			Epidermoid (18)	*Oat-cell or anaplastic (38)*	*Adenocarcinoma (10)*
		Nonsmokers	61.1 (11)	31.6 (12)	50.0 (5)
		Smokers:			
		<5 cigarettes/day	5.6 (1)	15.8 (6)	20.0 (2)
		5–14	22.2 (4)	23.7 (9)	10.0 (1)
		15–25	5.6 (1)	18.4 (7)	...
		>25	5.6 (1)	10.5 (4)	20.0 (2)
					Males—105 unclassified tumors. Females—13 unclassified tumors.

TABLE 6. *Epidemiologic and pathologic investigations concerning smoking and the histology of lung cancer*[1] (cont.)
(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of persons and case selection method	Results	Comments
Breslow et al., 1954, U.S.A. (42).	493 male and 25 female cases with histologically proven lung cancer. 518 age and sex-matched controls.	*Percent of patients with specific lung cancers by tobacco usage during the 20 years prior to study* All lung cancers other than adenocarcinoma (472): Nonsmokers 5.9; Cigarette smokers 94.1 Adenocarcinoma (46): Nonsmokers 13.0; Cigarette smokers 87.0 Controls (518): Nonsmokers 24.4; Cigarette smokers 75.6	Nonsmokers include pipe and cigar smokers only. The authors conclude that cigarette smoking appears to affect the development of epithelial carcinoma more than that of adenocarcinoma.
Schwartz et al., 1957, France (247).	430 male and female cases with histologically confirmed lung cancer. 4 matched control groups.	*Percent of smokers by histologic type and smoking history* Epidermoid: Cases 96.0; Controls 79.0† Anaplastic: Cases 97.0; Controls 83.0† Unknown type: Cases 96.0; Controls 79.0† Cylindrical: Cases 100.0; Controls 96.0	† Difference significant at $p \leqq 0.05$ level.
Haenszel et al., 1958, U.S.A. (113).	158 female cases of lung cancer.	*Relative risk for specified tumors (smokers/nonsmokers)* Adjusted for age and occupation: Group I (Kreyberg) 3.0†; Adenocarcinoma 1.19	134 cases with final histological determination. † Difference from unity significant at $p \leqq 0.01$.
Haenszel and Shimkin, 1962. U.S.A. (112).	2,191 male cases of lung cancer with adequate histologic data.	*Standardized mortality ratios* White males total: Epidermoid and undifferentiated carcinomas 100; Adenocarcinoma 100 Never smoked: 6; 18 Ex-smokers: 34; 46 <1 pack/day: 123; 116 >1 pack/day: 499; 467	Cases obtained from a 10 percent sample of lung cancer deaths in U.S.A. during 1958. The authors noted an absence of important differentials by histologic type.

TABLE 6.—*Epidemiologic and pathologic investigations concerning smoking and the histology of lung cancer*[1] *(cont.)*

(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of persons and case selection method	Results					Comments
Cohen and Hossain, 1966, U.S.A. (*58*).	417 male and female cases of lung cancer with histologic diagnosis 1939–63 at one hospital.		*Percent cases by histologic type and smoking history (number of smokers)*				The authors also noted that: 1. Adenocarcinomas were 2½–3 times more common in women 2. Only 1 percent of Kreyberg Group I cases were nonsmokers.
			Squamous	*Undifferentiated*	*Adenocarcinoma*	*Alveolar*	
		Nonsmokers	1.0 (3)	10.0 (17)	23.0 (8)	20.0(1)	
		Smokers	89.0(183)	90.0(146)	60.0(20)	...	
Ashley and Davies, 1967, England (*6*).	442 male and female cases of histologically diagnosed lung cancer.		*Percent cases by histologic type and smoking history*				The authors noted that cigarette smoking appears to be as strongly related to adenocarcinoma as to the other 2 types. Ashley's data on total number of cigarette smokers are inconsistent with his breakdown of smokers into groups based on number of cigarettes smoked per day.
			Undifferentiated	*Squamous*	*Adenocarcinom*		
		Nonsmokers	2.8 (4)	2.5 (6)	3.4 (2)		
		Pipe	9.9 (14)	9.9 (24)	1.7 (1)		
		Cigarette	87.3(124)	87.6(211)	94.9(56)		
		<10/day	14.1 (20)	22.4 (54)	22.0(13)		
		10–20	33.8 (48)	41.5(100)	33.9(20)		
		21–30	12.0 (17)	21.6 (52)	16.9(10)		
		31–40	14.1 (20)	12.9 (31)	8.5 (5)		
		>40	7.1 (10)	6.2 (15)	5.1 (3)		
Ormos et al., 1969, Hungary (*204*).	118 male and female cases of histologically proven lung cancer with adequate smoking information.		*Percent cases by histologic type and smoking history*				The author noted that the small number of cases allows for no definite conclusions.
			Group I	*Group II and large cell carcinomas*			
		Nonsmokers	21.0(18)	36.0 (9)			
		Smokers	79.0(68)	64.0(16)			

[1] Data obtained from patient interview and other sources.

TABLE 8.—*Tumor prevalence among males and females 35–69 years of age, by type of tumor and smoking category*
(Smokers constituted 86 percent of populations studied)

Sex and type of tumor	Smoking category			Expected number among smokers [1]	Risk ratio among smokers
	Total	Smoking all methods	Non-smokers		
Males					
Epidermoid carcinoma	434	431	3	17.0	25.4
Small cell anaplastic carcinoma	117	116	1	5.7	20.4
Adenocarcinoma	88	83	5	28.3	2.9
Bronchiolol-alveolar carcinoma	....	....	...	....	....
Carcinoid	46	39	7	39.7	1.0
Bronchial gland tumor	....	....	...	....	....
Total	685	669	16	90.7	7.4
Females					
Epidermoid carcinoma	12	9	3	.75	12.0
Small cell anaplastic carcinoma	8	5	3	.75	6.6
Adenocarcinoma	56	14	42	10.5	1.3
Bronchiolol-alveolar carcinoma	....	....	...	....	....
Carcinoid	32	7	25	6.3	1.1
Bronchial gland tumor	....	....	...	....	....
Total	108	35	73	18.3	1.9

[1] Number that would be expected if incidence rate among smokers were equal to that of nonsmokers.

SOURCE: Kreyberg, L. (*154*)

Lung Cancer Relationships in Women

Lung cancer death rates for women are presently much lower than the corresponding rates for men. In addition, it has been observed that among certain strains of mice exposed to carcinogenic agents, the male animals show a greater tendency to develop lung tumors than do the females (*200, 307*) although there are strains for which this is apparently not so. The extent of the influence of endocrine factors in the sex variation in the incidence of lung tumors is unknown.

As of 1967 in the United States, women accounted for only about one-sixth of the total deaths from lung cancer (*289*). However, the lung cancer death rate in women has risen by over 400 percent in the past 40 years. From 1950 to 1967 alone, the rate per 100,000 population doubled, increasing from 4.5 to 8.9 (*289, 290*).

A number of retrospective studies concerning lung cancer and cigarette smoking among women have found that the difference in the prevalence of lung cancer between males and females is accounted for principally by those tumors classified as Kreyberg's Group I (*154, 311*). These, as was noted above, are the tumors, particularly in males, which show the closest relationship with smoking. Haenszel, et al. (*113*), in a study of 158 women with lung cancer, observed that the sex differential for lung cancer death rates diminishes, but does not fully disappear when only nonsmokers are considered.

Hammond (*118*) found that the death rate for lung cancer in nonsmoking males was somewhat higher than for nonsmoking females. However, the difference in male-female rates was much greater when smokers were compared. It appears that a substantial part of the difference in death rates between male smokers and female smokers can be explained mainly by differences in their smoking habits.

These differences in smoking habits between males and females are of two types. First, overall consumption among females is still significantly lower than that among males. In 1966 (*281*), 30 percent of males reported that they had never smoked while for females the corresponding figure was 59 percent. This study also noted that nearly three times as many males as females reported consuming more than 20 cigarettes per day. Second, it has been shown that women smoke differently than men (*303*) : They begin smoking later than men (*114*) and do not smoke cigarettes as close to the end, where proportionally more nicotine and "tar" are inhaled. Women smoke more filter-tip and "low tar and nicotine" cigarettes than men. Furthermore, cigarette smoking still tends to be heavily concentrated among women under the age at which lung cancer is most likely to occur.

Finally, analysis of the ratio of male and female lung cancer death rates (*283, 284, 285, 286, 287, 288, 289, 290*) reveals that since 1960 this ratio has shown a steady decline, reflecting the greater relative rise in mortality from lung cancer in the female population.

Lung Cancer, the Urban Factor, and Air Pollution

A number of studies have been concerned with the relative influences of smoking, urban residence, and air pollution in the etiology of lung cancer. Table 9 lists studies performed in the United States, Great Britain, and Japan which have dealt with this question. Kotin and Falk (*149, 150*) and more recently the Royal College of Physicians (*228*) have reviewed the literature concerning the influence of atmospheric and environmental factors in the pathogenesis of lung cancer.

The studies listed in table 9 show a number of important trends. Lung cancer death rates are found to be higher among urban populations than among rural populations. It is not known to what extent this urban factor in the etiology of lung cancer is due to differences in the levels of air pollution. Other factors associated with urban residence which may influence the etiology of lung cancer are: differences in smoking habits between the two populations, occupational differences, and possible differences in the reporting of lung cancer deaths (*228*).

The studies also uniformly show that within each urban/rural grouping, lung cancer death rates increase with increased smoking. Whether air pollution acts with cigarette smoking to influence lung cancer death rates in a combined manner is presently unclear (*112, 126, 264, 265*), and the evidence concerning a separate role of air pollution in the etiology of lung cancer is still inconclusive (*228*).

The recent report of the Royal College of Physicians on air pollution and health (*228*) concluded that "the study of time trends in the death rates of lung cancer in urban areas demonstrates the overwhelming effect of cigarette smoking on the distribution of the disease. Indeed, only the detailed surveys that have taken individual smoking histories into account have succeeded in separating the relatively very small influence of the 'urban factor' on the overriding effect of cigarette smoking in the development of cancer of the lung."

TABLE 9.—*Epidemiologic investigations concerning the relationship of lung cancer to smoking, air pollution, and urban or rural residence*

(Actual number of deaths shown in parentheses)

Author, year, Country, reference	Population studied and method of data collection	Results	Comments
Doll, 1953, England (70).	Estimated death rates from lung cancer in English population and among nonsmokers obtained from general register.	*Lung cancer mortality (1950) per 1,000* *Males*: *London*; *Other urban*; *Rural* *Females*: *London*; *Other urban*; *Rural* *Nonsmokers*: *All areas* Age: 25–44 ..... 0.126; 0.095; 0.070; 0.028; 0.028; 0.012; 0.020 45–64 ..... 1.572; 1.264; 0.851; 0.194; 0.152; 0.120; 0.090 65–74 ..... 3.124; 2.006; 1.104; 0.440; 0.326; 0.288; 0.219	Authors noted that estimates are based on very few deaths.
Stocks and Campbell, 1955, England (255).	Death rates in England and Northern Wales. Review of patient chart or interview with kin or physicians.	*Male lung cancer death rates 1952–54 (per 100,000) ages 54–74* *Rural (68)*; *Mixed (118)*; *Urban (539)* Nonsmokers ..... 14; ..; 131 Pipe ..... 41; 25; 143 Cigarettes: Light ..... 87; 153; 297 Moderate ..... 183; 132; 287 Heavy 363; 303; 304	The authors noted the upward gradient among nonsmokers, pipe smokers and light cigarette smokers and the lack of a similar gradient among moderate and heavy cigarette smokers.
Hammond and Horn, 1958, U.S.A. (120).	187,783 white males in 9 states. Questionnaire and interview.	*Age standardized death rates due to bronchogenic carcinoma (males)* *Rural*; *Suburb or town*; *City of 10,000–50,000*; *City of >50,000* Nonsmokers ....; 4.7 (2); 9.8 (8); 14.7 (4) Cigarette smokers 65.2 (52); 71.7 (67); 70.9 (59); 85.2 (83)	Data excluded adenocarcinoma. when standardized for age and smoking, rural rate was still noted to be 25 percent less than urban.

TABLE 9.—*Epidemiologic investigations concerning the relationship of lung cancer to smoking, air pollution, and urban or rural residence (cont.)*

(Actual number of deaths shown in parentheses)

Author, year, Country, reference	Population studied and method of data collection	Results	Comments
Haenszel et al., 1962, U.S.A. (*118*).	10 percent of all white male lung cancer deaths in U.S.A. for 1958 for whom next of kin or physicians supplied smoking data. 2,191 cases with adequate information.	*Age- and smoking-standardized lung cancer mortality ratios (epidermoid and undifferentiated carcinomas only)* *Metropolitan counties*: >50,000 .....119; 10,000–50,000 .....151; 2,500–10,000 .....99 *Nonmetropolitan counties*: 2,500–50,000 .....90; Rural nonfarm ....74; Farm 57	Standardized Mortality Ratio = *100* for U.S. white males age 35 and over in 1958. The authors also noted "... joint effects of residence and smoking histories in the schedule of lung-cancer rates far greater than those expected on the assumption of additivity of the separate effects ..."
Doll and Hill, 1964, England (*74*).	41,000 male British physicians. Questionnaire and follow-up of death certificate.	*Standardized death rates for lung cancer* Nonsmokers: Conurbation (*49*) 0.03; Large Towns (*34*) 0.00; Small Towns (*32*) 0.11; Rural (*18*) 0.12 Cigarette smokers: 1–14: 0.48; 0.32; 0.87; 0.52 15–24: 1.31; 1.88; 1.06; 1.15 >25: 1.90; 4.43; 2.20; 1.17	The authors noted that rural mortality data were affected by a significant number of city residents retiring to the country.
Wicken, 1966, Northern Ireland (*308*).	1,908 male and female lung cancer deaths over 35 years of age from register. Personal interviews with kin or physicians.	*Lung cancer death rate per 100,000—age- and smoking-standardized* Males: Inner Belfast 157 (241); Outer Belfast 139 (157); Belfast Environs 135 (45); Urban Areas 118 (185); Small Towns 137 (26); Rural 47 (149) Females: 22 (38); 17 (24); 12 (6); 23 (35); 22 (5); 12 (43)	Total number of deaths noted under method of data collection include 954 controls.

TABLE 9.—*Epidemiologic investigations concerning the relationship of lung cancer to smoking, air pollution, and urban or rural residence (cont.)*

(Actual number of deaths shown in parentheses)

Author, year, Country, reference	Population studied and method of data collection	Results	Comments
Buell et al., 1967, U.S.A. (*149*).	804 lung cancer deaths among American Legionnaires aged 25 and over. Questionnaires to next of kin.	*Age-adjusted lung cancer death rates per 100,000 man years and mortality ratios* Los Angeles: Rate / Ratio; San Francisco/San Diego: Rate / Ratio; All other California counties: Rate / Ratio Nonsmokers: 28.1 / 2.5; 43.9 / 3.9; 11.2 / 1.0 Smokers: <1 pack/day: 63.6 / 5.7; 77.1 / 6.9; 61.02 / 5.4 ±1: 126.0 / 11.8; 134.5 / 12.0; 124.9 / 11.2 >1: 241.3 / 21.5; 226.0 / 20.2; 137.5 / 12.3	The authors noted the lack of death-rate difference between Los Angeles and San Francisco regions and concluded that photochemical smog is not related to lung cancer.
Hitosugi, 1968, Japan (*118*).	185 male and female lung cancer deaths and 4,191 matched controls aged 35–74. Data from questionnaires and interviews.	*Lung cancer death rate per 100,000* Pollution region: Low / Intermediate / High *Males* Nonsmokers: 11.5 / 8.8 / 4.9 Smokers: 1–14 cigarettes/day: 10.6 / 14.2 / 28.5 >15: 21.3 / 18.6 / 31.4 *Females* Nonsmokers: 4.6 / 6.9 / 3.8 Smokers: 1–14 cigarettes/day: 19.7 / 16.5 / 15.3 >15: 12.4 / 20.5 / 17.1 *Age- and smoking-adjusted lung cancer death rate per 100,000* Low / Intermediate / High Males: 16.1 / 22.4 / 28.4 Females: 7.5 / 11.6 / 8.7	The authors postulated a slight synergistic effect between smoking and air pollution.

Uranium Mining

The excess risk for the development of lung cancer among uranium and fluorspar miners has been known for more than 30 years. In a recent review, Bair (*17*) noted that radon and radon-decay products are the only inhaled radionuclides to be epidemiologically related to lung cancer. Lundin, et al. (*178*), in a continuation of the work initiated by Wagoner, et al. (*299, 300, 301*), have recently reported on a 17-year follow-up of 3,414 white underground uranium miners. The authors estimated that smoking uranium miners experienced an excess of lung cancer ten times greater than did nonsmoking miners.

Saccomanno (*231*), in recent testimony, analyzed the data of the United States Public Health Service (USPHS) Study Group as presented by Lundin, et al. (*178*) above. He reported that cigarette smoking uranium miners incurred lung cancer rates four times greater than those of other cigarette smokers.

Of the 62 lung cancer deaths in this population, 60 occurred in smokers. He also observed that among 100,000 uranium miners 700 lung cancer deaths per year would be expected to occur among cigarette smokers compared with only 4 among nonsmokers.

Other Occupations

Nelson (*199*) has recently reviewed certain environmental and occupational hazards as they relate to inhalation carcinogenesis. He observed that cancer of the respiratory tract has been linked epidemiologically and, in some cases, experimentally with occupational exposure to the following materials: chromium, nickel, arsenic, and asbestos. Doll (*72*) and Goldblatt (*100*), in earlier reviews, also noted an association with coal, natural gas, and graphite exposures.

Nickel

Morgan (*194*) noted that much of the nasal and lung cancer attributed to nickel exposure may have been due to arsenical impurities found in processed nickel prior to 1925. Doll (*69*) found that the number of excess deaths among nickel workers under 50 years of age had declined following the change in nickel manufacturing processes. The experiments of Hueper (*134*) and Sunderman, et al. (*267, 268, 269*) have shown that both guinea pigs and rats develop lung cancer following chronic exposure to nickel carbonyl or nickel dust. Sunderman and Sunderman (*270*) also reported that cigarette smoke contains nickel and that this concentration of nickel

may be capable of inhibiting the induction of lung aryl hydroxylase, an enzyme which is able to detoxify aromatic hydrocarbons including known carcinogens such as benzo[a]pyrene.

Asbestos

In 1955, Doll (*71*) found that lung cancer was a definite hazard among asbestos workers. In a more recent study, Selikoff, et al. (*251, 252*) examined the relationship of smoking and asbestos exposure to lung cancer. These authors followed 370 people who had been asbestos workers during the years 1942–1962. Over a 5-year follow-up period, 94 deaths occurred in this group, of which 24 were due to bronchogenic carcinoma. The authors noted that according to data obtained from Hammond (*118*), only 3.16 deaths from lung cancer would have been expected among smokers, and calculated a 7.6 to 1.00 mortality ratio due to asbestos exposure. None of the 87 nonsmokers or pipe and cigar smokers died of lung cancer. When the expected number of nonsmoker deaths (0.26) is compared with the actual number (*24*) which occurred among the smoking asbestos workers, an extremely high mortality ratio of 92 to 1 is obtained, thus reflecting the possible interaction of asbestos exposure and cigarette smoking.

Exposure of mice (*179*) and rats (*106*) to asbestos dust or the intratracheal injection of chrysotile asbestos dust has resulted in the production of significant numbers of primary pulmonary carcinomas. Miller, et al, (*184*) exposed hamsters to intractracheal injections of benzo[a]pyrene. These authors observed that the addition of the chrysotile variety of asbestos to the injections appeared to promote benzo[a]pyrene carcinogenesis in the respiratory tract, as determined by the time of appearance and yields of papillomas and carcinomas.

Arsenic

A recent epidemiologic study by Lee and Fraumeni (*163*) has indicated an excess of lung cancer deaths among smelter workers exposed to arsenic for more than one year. Cigarette smoking was not taken into account in their computations. Experimental work on the induction of cancer in animals using arsenic has yielded either negative or inconclusive results (*133, 135*).

Chromium

Exposure to industrial bichromate compounds has been associated with an excess of lung cancer deaths (*22,255*). Laskin, et al. (*159*) have recently reported that intrabronchial pellet implanta-

tion of various chromium compounds in rats is associated with the development of squamous cell carcinomas and adenocarcinomas. However, Nettesheim, et al. (*200*) exposed mice to chromium oxide dust and observed that it had no discernible effect on lung tumor incidence.

Pathological Studies

Investigators who have conducted detailed autopsy studies on patients who died of lung cancer have reported the increased presence, when compared to noncancer patients, of bronchial epithelial changes which they considered to be precursors of bronchogenic carcinoma (*7, 8, 23, 51, 104, 208, 220, 279, 309*). Such changes include squamous metaplasia, atypical squamous metaplasia (with acanthosis, dyskeratosis, and numerous mitotic figures), and carcinoma *in situ*. Carnes (*51*) noted that carcinoma *in situ* was present in 119 cases of lung cancer but not in any of the 119 controls who were matched for age, sex, and race.

Autopsy studies comparing the frequency of these cancer-related changes in the lungs of smokers and nonsmokers are presented in table 10. Virtually all the studies noted an increased prevalence of these epithelial alterations among smokers as compared with nonsmokers. Definite dosage-dependent relationships were evident in the results of many of the reports. Also, Auerbach, et al. (*14*) observed that the number of cells with atypical nuclei decreases progressively in the bronchial mucosa of ex-cigarette smokers, depending upon the number of years between cessation of smoking and death, although it usually remains above that found in nonsmokers.

The cytologic studies included in this table (*182, 198, 222*) all noted an increased percentage of sputum specimens showing metaplasia among smokers as compared with nonsmokers.

Pulmonary Carcinogenesis

General Aspects of Carcinogenesis

Agents found in cigarette smoke which have been identified as, or are suspected of being carcinogenic, are listed in table 11. The list includes certain compounds which most probably contribute to the pathogenesis of the various cancers discussed in the other sections of this chapter. Many other agents have been identified in tobacco and tobacco smoke. At the present time, they do not appear to bear a direct relationship to carcinogenesis. Stedman (*262*) and Wynder and Hoffmann (*319*) provide detailed listings and discussions concerning these materials.

TABLE 10.—*Pathologic and cytologic findings in the tracheo-bronchial tree of smokers and nonsmokers*
(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of cases and method of selection	Results					Comments
Chang, 1957, U.S.A. and Korea (*55*).	105 males and females 40–86 years of age.	*Percent of cases with bronchial basal cell hyperactivity*					Smokers included pipe and cigar smokers. † $p \leqq 0.01$ in comparison with nonsmokers.
		Nonsmokers				28.5 (34)	
		Smokers				43.7 (71)	
		Heavy smokers				†61.3 (31)	
Hamilton et al., 1957, U.S.A. (*117*).	Selected autopsy material.		*Number*	*Age range*	*Percent of cases with: Basal cell hyperplasia*	*Squamous metaplasia*	*Transitional metaplasia*	No lung cancer patients included.
		Smokers	15	39–77	86.6	20.0	40.0	
		Nonsmokers	20	28–83	40.0	15.0	35.0	
Sanderud, 1958, Norway (*240*).	100 males autopsied at Gade Institute on whom smoking data was available.	*Percent of cases with bronchial squamous epithelial metaplasia*					Nonsmokers include those smoking less than or equal to 5 grams per day.
		Nonsmokers				54.0 (39)	
		Pipe				80.5 (20)	
		All cigarette				79.0 (38)	
		Cigarettes per day:					
		5–14				70.0 (23)	
		15–25				90.0 (10)	
		>25				100.0 (5)	
Knudtson, 1960, U.S.A. (*147*).	100 persons 23–85 years of age autopsied at Seattle Veterans Hospital on whom smoking data was available.		*No. of Persons*	*No change*	*Percent of cases with: Basal cell hyperplasia*	*Squamous metaplasia*	*Atypical proliferative metaplasia*	Age, occupation, and site of residence were found to have no appreciable effect.
		Nonsmokers	(21)	47.6	28.6	14.3	9.5	
		Cigarettes/day:						
		1–9	(9)	77.8	11.1	11.1	..	
		10–15	(11)	18.2	18.2	54.5	9.1	
		16–20	(44)	20.4	29.5	29.5	20.5	
		>21	(9)	11.1	33.3	44.4	11.1	
		Pipe or cigar	(6)	..	100.0	..	..	

TABLE 10.—*Pathologic and cytologic findings in the tracheo-bronchial tree of smokers and nonsmokers (cont.)*
(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of cases and method of selection	Results						Comments
Auerbach et al., 1961, U.S.A. (*11*).	339 persons 22–88 years of age autopsied at East Orange Veterans Hospital (excludes lung cancer).		*Number of persons*	*Number of sections of bronchial epithelium*	*Percent sections with cilia absent and entirely atypical cells*	*Percent sections with some atypical cells and cilia absent*		The authors noted a dose-response relation of smoking to: a. loss of cilia, b. increase in number of atypical cells, c. carcinoma *in situ*. Average number of sections per case equaled 52.3.
		Nonsmokers:						
		<40 years of age	8	383	..	0.3		
		40–59	11	560	..	..		
		60–69	28	1,463	..	0.1		
		>70	18	918	..	0.5		
		Smokers <1 pack/day:						
		<40 years of age	14	727	0.1	4.7		
		40–59	24	1,240	1.0	16.9		
		60–69	35	1,772	0.5	10.8		
		>70	22	1,101	0.6	9.4		
		Smokers >1 pack/day:						
		<40 years of age	17	880	1.5	12.5		
		40–59	63	3,027	4.5	17.4		
		60–69	84	4,186	6.9	20.5		
		>70	15	756	9.8	23.7		
Cross et al., 1961, U.S.A. (*64*).	140 persons autopsied at Iowa City Veterans Hospital on whom smoking data was available.		*Percent sections showing changes in bronchial epithelium (number of sections)*					† The authors noted that the difference between smokers and nonsmokers was statistically significant.
			Normal	*Hyperplasia*	*Squamous metaplasia*	*Atypical metaplasia*	*Carcinoma in situ*	*Carcinoma*
		Nonsmokers (81)	61(562)	36(137)	8 (33)	†15 (58)	....	....
		Smokers (109)	44(570)	43(562)	16(197)	20(263)	1(12)	2.6(34)

TABLE 10.—*Pathologic and cytologic findings in the tracheo-bronchial tree of smokers and nonsmokers (cont.)*

(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of cases and method of selection		Number	Number of sections of bronchial epithelium	Percent sections with cilia absent and entirely atypical cells	Percent sections with some atypical cells and cilia absent	Percent sections with 50 percent atypical cells and cilia present	Comments
Auerbach et al., 1962. U.S.A. (*14*).	72 autopsied former cigarette smokers who had been smoking for ≧10 years and had ceased ≧5 years ago.	Nonsmokers	72	3,156	0.0	0.1	0.5	Each ex-smoker matched with a current smoker plus never-smoker for age, occupation, and residence. There was an average of 50.3 sections per subject and none had less than 18 sections.
		Ex-smokers	72	3,436	0.2	0.9	2.6	
		Current smokers	72	3,537	8.0	19.0	80.8	

TABLE 10.—*Pathologic and cytologic findings in the tracheo-bronchial tree of smokers and nonsmokers (cont.)*
(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of cases and method of selection	Results					Comments
			Number	*Number of sections of bronchial epithelium*	*Percent sections with cilia absent and entirely atypical cells*	*Percent sections with some atypical cells and cilia absent*	*Percent sections with 50 percent atypical cells and cilia present*	
Auerbach et al., 1962, U.S.A. (13).	456 male and 302 female smokers and nonsmokers autopsied and matched for age, occupation, and residence.	Males:						Major findings noted: Urban nonsmokers showed more lesion than rural. Both lesions and atypical nuclei were much less frequent in nonsmokers and less frequent in pipe and cigar smokers than in cigarette smokers. 57.1% of cases had 50–55 sections 31.5% of cases had 40–49 sections 7.3% of cases had 30–39 sections 4.6% of cases had 16–29 sections
		Nonsmokers	47	2,346	..	0.1	0.7	
		Cigarette smokers	75	3,393	6.9	21.2	78.5	
		Females:						
		Nonsmokers	47	2,379	..	0.1	0.5	
		Cigarette smokers	75	3,507	2.5	18.8	62.6	
		Males:						
		Nonsmokers	35	1,706	..	0.2	0.5	
		Cigar smokers	35	1,733	0.3	10.0	10.7	
		Cigarette smokers	35	1,526	12.8	27.3	83.1	
Robbins, 1966, U.S.A. (222).	103 students 17–24 years of age who underwent aerosol sputum induction.			*Percent in each cytologic class*				Smokers defined as those having consumed ≥10 cigarettes a day for ≥1 year.
				Normal	*Slightly atypical*	*Moderately atypical*	*Strongly atypical*	
		Nonsmokers (45)		86.7	4.4	8.9	..	
		Smokers (58)		55.2	32.8	10.3	1.7	

TABLE 10.—*Pathologic and cytologic findings in the tracheo-bronchial tree of smokers and nonsmokers (cont.)*

(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of cases and method of selection	Results					Comments
Maltoni et al., 1968, Italy (*182*).	1,000 healthy males who underwent sputum induction.			*Number*	*Percent showing metaplasia*		
		Nonsmokers		204	41.16		
		Smokers:					
		1–10 cigarettes/day		189	47.09		
		11–20		886	51.43		
		21–30		93	61.29		
		>30		39	69.23		
Nasiell, 1968, Sweden (*195*).	50 nonsmoking outpatients, 398 smokers participating in general health examination who underwent sputum induction.	*Sputum cytologic changes*					† Regarded by author as "real premalignant change."
			Number	*Percent Males*	*Mean age*	*Percent with metaplasia*	*Percent with atypical metaplasia*†
		Nonsmokers	50	42	57.1	18	4
		Smokers	398	73	46.6	62	27
Spain et al., 1970, U.S.A. (*258*).	157 males and 78 females autopsied following sudden or accidental death for whom smoking data were available (ex-smokers excluded from female data).			*Number*	*Percent with metaplasia*		The authors found no evidence of carcinoma *in situ* or preneoplastic atypical changes.
		Males:					
		Nonsmokers		36	50.0		
		Ex-smokers		21	57.7		
		<1 pack		32	62.5		
		>1 pack		68	73.5		
		Females:					
		Nonsmokers		34	34.1		
		<1 pack		18	33.3		
		>1 pack		26	46.1		

In order to facilitate understanding of the relationships of the various compounds to one another, the third column presents the presently understood relative importance of each of the various groups of compounds. These compounds have been tested only in animals or tissue cultures, and it should be stressed that the relative importance of one compound may not be the same in man as it is in animals.

Table 11 is divided into two major sections. The first section details those compounds which are considered to be or are suspected of being cancer initiators. These are compounds which induce irreversible changes in responsive cells. In the second section are listed those compounds which are considered to be or are suspected of being tumor promoters. These compounds promote the malignant reproduction of cells in which neoplastic changes have been initiated. A number of these initiators may also act as complete carcinogens in their own right. The evidence concerning the two stage initiation-promotion mechanism is still rather limited for respiratory tract carcinogenesis.

The *polynuclear aromatic hydrocarbons* (PAH) listed are presently considered to play a very significant role in pulmonary carcinogenesis due to tobacco smoking. These compounds act as tumor initiators or complete carcinogens. The particular role of these agents in environmental and occupational carcinogenesis has been reviewed by Falk, et al. (*93*). That such hydrocarbons are produced from tobacco during human smoking has been shown by Kiryu and Kuratsune (*146*). These authors reported the presence of benz[a]anthracene, chrysene, benzo[a]pyrene, and benzo[b]fluoranthene in the "tar" produced by normal smoking and measured in either filters or stubs.

Two hydrocarbons which have frequently appeared in the literature on experimental tobacco carcinogenesis may not actually be present in tobacco smoke. They have been used as representatives of carcinogenic PAH, a class which includes many constituents that have been identified in cigarette smoke condensate. They are 7,12-dimethylbenz[a]anthracene and 3-methylcholanthrene and have been frequently used as tumor initiators or complete carcinogens, particularly in skin painting and tracheal implantation experiments.

The *nitrosamine compounds* listed are potent carcinogens affecting many organ systems, including the respiratory tract (*188, 189*). Magee and Barnes (*181*) have presented a detailed account of experiments in this area. Nitrosamines have been identified in trace amounts in tobacco "tar" and the conditions required for their formation (the presence of secondary amines and nitric oxide) are

TABLE 11.—*Identified or suspected tumorigenic agents in cigarette smoke*[1]

Components	Estimated concentration in 100 cigarettes (85 mm. nonfilter)	Presently understood relative importance in experimental tobacco carcinogenesis
I. Complete carcinogens and tumor initiators:		
Polynuclear aromatic hydrocarbons	10-30 ug	Tumor initiators.
1. Benzo(a)pyrene	3.9	
2. Dibenz(a,h)anthracene	0.4	
3. Benzo(b)fluoranthene	0.3	
4. Benzo(j)fluoranthene	0.6	
5. Dibenzo(a,i)pyrene	Trace	
6. Benz(a)anthracene	0.3	
7. Chrysene	2.0	
8. Indeno(1,2,3-cd)pyrene	0.5	
9. Benzo(c)phenanthrene[2]	Trace	
10. Methylbenzo(a)pyrenes	0.1	
11. Methylchrysenes	2.0	
N-heterocyclic hydrocarbons	1-2	Tumor initiators.
1. Dibenz(a,h)acridine	0.01	
2. Dibenz(a,j)acridine	1.0	
3. 7H-dibenzo(c,g)carbazole	0.07	
N-nitrosamines[3]	1-10	*Suspected carcinogens of possible importance (presence in fresh smoke possible).*
1. Dimethylnitrosamine	0.4	
2. Diethylnitrosamine	Trace	
3. Methyl-n-butylnitrosamine	Trace	
4. Nitrosopyrrolidine	0.4	
5. Nitrosopiperidine	Trace	
Epoxides, peroxy compounds, and lactones:		
1. Epoxides	No data	Certain of these compounds are known carcinogens; presence in smoke condensate not established.
2. Peroxides	Present	
3. Lactones	....	
a. α-Levantenolide	20.0	
b. β-Levantenolide	2.0	
N-alkyl-heterocyclics:		
1. 1-methylindole	Present	Possible initiator.
Pesticides and fungicides:[4]		No essential contribution suspected.
1. TDE	10-100	
2. o,p'-DDD	10-100	
3. DDT	10-100	
4. Maleic hydrazide	10-100	
Beta-naphthylamine	2-3	Suspected bladder carcinogen; of doubtful significance at reported levels.
Polonium 210	1-50 picocuries	*Of some importance only in the case of relatively high concentration, but not important at reported levels.*
Nickel compounds	Present	Suspected carcinogens of some importance.

TABLE 11.—*Identified or suspected tumorigenic agents in cigarette smoke*[1] *(cont.)*

Components	Estimated concentration in 100 cigarettes (85 mm. nonfilter)	Presently understood relative importance in experimental tobacco carcinogenesis
II. Tumor promoting agents:		
Neutral promoters (polymers) (unknown structures.)	No data	Of possible importance.
Volatile phenols	20-30 mg.	Of possible importance.
1. Phenol		
2. Cresol		
Nonvolatile fatty acids	20-100 mg.	Of minor importance.
1. Stearic acid		
2. Oleic acid		
N-alkyl heterocyclics:		Of possible importance.
1. 9-methylcarbazole	Present	

[1] Modified and expanded from (*319, 320*) with reference to (*52, 60, 89, 111, 129, 202, 262, 293, 294, 295*).
[2] Has not been tested as an initiator, but is a known complete carcinogen.
[3] See Neurath, (*202*).
[4] See (*111, 128*).

found in tobacco smoke (*38*). However, nitrosamines may be artifacts dependent on the method of smoke collection (*201*).

Neurath (*202*) considers the nitrosamines listed in table 11 as being present in fresh cigarette smoke (*253, 254*). However, conclusive confirmation of their presence in fresh smoke is not available (*38, 138, 155, 319*).

Certain of the *pesticides* and *fungicides* presently in use on tobacco have been found to be carcinogenic (*91, 273, 280*). A number of these, such as DDT, are now being phased out of regular domestic use. The compounds listed have been shown to be present in trace amounts in mainstream tobacco smoke (*111, 128*). A recent, extensive review by Guthrie (*111*) provides more detailed information concerning these agents.

Radioactive isotopes can be found in tobacco and tobacco smoke (*105*). Potassium-40, while present in tobacco leaf, is not transmitted in any substantial amount to mainstream smoke (*230*). Polonium-210 (Po_{210}), however, is transmitted into the mainstream smoke (*94, 123, 142, 145, 215, 217*). A number of autopsy studies (table A12) have shown that the bronchial epithelium of smokers contains significantly more Po_{210} than that of nonsmokers. Little, et al. (*172, 173, 174*) have also noted that the concentration of polonium was markedly higher at sites of bronchial bifurcation. These authors stress the importance of this finding for pulmonary carcinogenesis by noting that bronchogenic carcinomas are fre-

quently located at bifurcations and that the polonium levels which they found in those regions probably have biologic significance (*216*). Other investigators (*123, 217*) have not observed this excess at bifurcations, and in a recent discussion Wynder and Hoffmann (*320*) concluded that it appears unlikely that Po_{210} in the amounts present in cigarette smoke plays a role in tobacco carcinogenesis.

Although not listed as a separate group, there are a number of agents in cigarette smoke which are potent inhibitors of ciliary movement. Their importance in carcinogenesis derives from the increased amount of time which they afford the known carcinogens to be present on the surface of the bronchial epithelium. These inhibitors include volatile aldehydes, hydrogen cyanide, nitrogen oxides, volatile phenols, and certain volatile acids such as formic and acetic (*129*).

Experimental Studies

In some respects, the animal and tissue culture studies detailed below apply to neoplastic transformations, not only in the lung but in other tissues in which tobacco smoke, particularly cigarette smoke, is believed to play a role. These general experiments will be presented here, however, with the experiments which bear on lung tissue directly.

Skin Painting and Subcutaneous Injection

Numerous animal studies on rats, mice, and rabbits, have been performed utilizing known carcinogens, whole tobacco "tar," and various tobacco condensate subfractions, or compounds known to be present in tobacco smoke. These experiments involve the single or repeated painting of shaved or unshaved animal skin. A selected number of these studies is presented in table A13. Numerous other studies, performed prior to and following 1953, are reviewed by Wynder and Hoffmann (*319*).

The skin painting method is still considered to be a valid procedure for the identification of agents suspected of participating in pulmonary carcinogenesis, as well as for the quantification of the reduction in tumorgenicity of specific agents.

Tissue and Organ Culture

The exposure of tissue and organ cultures to cigarette smoke, its condensates, or its constituent compounds has been shown to significantly alter patterns of cell growth and reproduction. Table A14 presents an outline of these experiments. Once again, less severe effects have been noted when filtered smoke was used (*165*).

Tracheobronchial Implantation and Instillation

More complex experiments concerning the carcinogenicity of cigarette and tobacco smoke are represented by those which involve the direct implantation, instillation, or fixation of suspected materials into the tracheobronchial tree of animals. Certain of these experiments are outlined in table A15. Recent reviews by Saffiotti (*233, 234*) Laskin, et al. (*159*), and Montesano, et al. (*189*) as well as that by Wynder and Hoffmann (*319*) provide more detailed and extensive accounts of these experiments.

Of note among the results outlined in this table are the following: The enhanced carcinogenicity found when benzo[a]pyrene (B[a]P) is combined with a carrier such as hematite dust (*235*), and the definite increase in bronchial epithelial preneoplastic and neoplastic changes among dogs treated with smoke condensate as compared with those undergoing only physical bronchial stimulation (*224*).

Inhalation

Various species, including mice, rats, hamsters, and dogs, have been exposed to cigarette smoke or aerosols of its constituents. These inhalation experiments are outlined in table A16. It must be noted that the majority of the studies listed involve the passive inhalation of the material presented usually in a chamber. Active inhalation experiments, exemplified by the work of Rockey and Speer (*223*) and Auerbach and his colleagues (*11, 119*) involved animals which were trained to inhale voluntarily, thus more closely simulating human smoking.

Results of note among these experiments include the following: Mühlbock (*195*) observed that cigarette smoke inhalation enhances the already substantial rate of spontaneous alveolar cell carcinoma formation in hybrid mice, and various investigators induced adenomas in experimental animals (*108, 168, 206*). Harris and Negroni (*121*) found that exposure to cigarette smoke achieved some enhancement of adenocarcinoma formation in mice but did not observe proven squamous cell carcinoma. Some of their mice had also been exposed to Swine influenza virus aerosol. In a related study, Boren (*32*) exposed hamsters to cigarette smoke at set intervals over a 48-hour period. The author observed alterations in pulmonary cell kinetics (the pattern of DNA synthesis) as demonstrated by H^3-thymidine autoradiography. The pattern of the labeling response to cigarette smoke was significantly different from that of the response to high oxygen concentrations.

Auerbach, et al. (*11*) have reported the development of early

invasive squamous cell bronchogenic carcinoma in dogs following a period of direct inhalation of cigarette smoke. These investigators trained beagle dogs to inhale cigarette smoke through a tracheostoma (*50*) and divided the animals into groups according to dosage as detailed in table 17. A number of dogs died during the course of the experiment which ran for 875 days, or approximately 29 months. The causes of death are listed in table 18. All of the remaining dogs, with the exception of group "h" (high exposure, heavy weight), were sacrificed shortly after day 875; the survivors among the heavier dogs are continuing to smoke.

Examination of the respiratory tree of the animals revealed a number of tumors (table 19). Most of these were similar to the type of tumor which in man is referred to as bronchiolo-alveolar. This tumor arises in the bronchiolar and alveolar epithelium and tends to be multicentric. Two striking characteristics of these bronchiolo-alveolar tumors were the existence of a histologic spectrum (from a tumor resembling the benign condition of adenosis to frankly malignant tumors with invasion of the pleura and surrounding parenchyma) and the marked tendency to squamous change. Invasive bronchiolo-alveolar tumors were found in 12 dogs in the group which had been exposed to the largest dosage of cigarette smoke. Several had tumors of more than one category. Ten of these dogs had invasive bronchiolo-alveolar tumors which did not extend into the pleura, one dog had an invasive bronchiolo-alveolar tumor which extended to the pleura, and four had invasive bronchiolo-alveolar tumors extending into the pleura beyond the pleural-pulmonary junctions. In addition, two bronchogenic squamous cell carcinomas were found in this group (table 19). The dosage dependence of tumor formation is shown in figures 2 and 3.

Major findings of the study were twofold. First, that smoking filter-tip cigarettes was less harmful, both in terms of pulmonary parenchymal damage and lung tumors, than smoking identical cigarettes without filters. This supports the generally held view that total particulate matter is a meaningful indicator of the carcinogenic potential of a cigarette. Second, lung cancer of two types found in man was produced by the inhalation of cigarette smoke. Two of the dogs were found to have early invasive squamous cell carcinoma of the bronchus, and both belonged to the high-dosage group. These carcinomas were indistinguishable from early invasive squamous cell carcinomas found in the bronchial tubes of human beings who smoke cigarettes. The majority of tumors found in the dogs were of a bronchiolo-alveolar type, which although not as common as squamous cell cancer in man, is not rare in humans. This type is often included in the category of adenocarcinoma. A number of studies have shown an excess of these tumors among

TABLE 17.—*Data on pedigreed male beagle dogs of groups F, L, H, h, and N*
(Some of the figures apply only to dogs surviving 875 days or longer)

	Filter group F	No filter group L	No filter group H	No filter group h	Nonsmokers group N
Number of dogs on day No. 57[1]	12	12	24	38	8
Weight at start (day No. 1) mean weight (pounds)	25.0	25.1	26.0	31.9	30.7
Cigarettes per dog in 875 days	6,143	3,103	6,129	6,129	none
Mean number of cigarettes per day	7.02	3.54	7.0	7.0	—
Equivalent number of cigarettes per day for 150 pound man	42.1	21.2	42.0	32.9	—
Type of cigarettes:[2]					
Milligrams of tar per cigarette	17.8	34.8	34.8	34.8	—
Milligrams of nicotine per cigarette	1.17	1.85	1.85	1.85	—
Total dosage in 875 days:					
Grams of tar per dog	109.3	103.5	207.8	207.8	—
Grams of nicotine per dog	7.19	5.56	11.12	11.12	—
Dosage in 875 days relative to starting weight:					
Grams tar/pounds weight	4.37	4.12	8.31	6.51	—
Grams nicotine/pounds weight	0.29	0.22	0.44	0.35	—

[1] The smoking dogs were divided into groups F, L, H, and h on day No. 57.
[2] Dogs of groups L, H, and h smoked filter-tip cigarettes during a training period at the start of the experiment, but smoked nonfilter cigarettes thereafter.
SOURCE: Adapted from Hammond, E. C. et al. (*119*).

TABLE 18.—*Summary of principal cause of death (days No. 57 through No. 875) in dogs of groups F, L, H, h, and N*

(Each death classified according to most severe condition—some dogs died of a combination of causes listed)

Principal cause of death	Filter tip Group F	No filter Group L	No filter Group H	No filter Group h	Nonsmokers Group N	Total
Pulmonary emphysema and fibrosis	—	—	2	—	—	2
Cor pulmonale (pulmonary emphysema and fibrosis with right heart enlargement)	—	—	3	5	—	8
Pulmonary infarction	1	1	2	5	—	9
Bronchopneumonia	—	—	3	1	—	4
Aspiration of food	1	1	—	—	—	2
Uncertain	—	—	2	1	—	3
Number of deaths	2	2	12	12	—	28
Number surviving 875 days	10	10	12	26	8	66
Total number of dogs	12	12	24	38	8	94

SOURCE: Hammond, E. C. et al. (*119*).

TABLE 19.—*Data on dogs with lung tumors indicating type of tumor and lobe in which the tumor was found*

Group		Day of death	Number of cigarettes	Age at death (years)	Lobes with bronchiolo-alveolar tumors Non-invasive	Invasive	Early squamous cell bronchial carcinoma
Group N (nonsmokers)	N	904a	—	5.1	LA	—	—
	N	904b	—	4.9	RA	—	—
Group F (filter-tip)	F	878a	6,161	5.1	LA	—	—
	F	879a	6,170	4.7	LA	—	—
	F	885a	6,224	5.2	LA	—	—
	F	890a	6,269	5.4	LA	—	—
Group L (no filter)	L	347	1,055	3.8	LA, LC	—	—
	L	812	2,847	5.1	RA	—	—
	L	876a	3,103	5.1	LA, RA	—	—
	L	877a	3,107	5.2	LA, LC	—	—
	L	882a	3,127	5.2	LA, LD	—	—
	L	890a	3,183	5.3	LA, RD	—	—
	L	899a	3,196	6.4	LA	—	—
Group H (no filter)	H	136	518	2.6	RC	—	—
	H	269	1,343	3.3	LA, RA, RD	—	—
	H	563	3,404	4.7	LD, RA	—	—
	H	716	4,689	5.0	..	LA	—
	H	753	5,030	3.8	RI	LA, RA, RD	—
	H	760	5,088	4.2	LA	—	—
	H	868	5,970	5.3	LA	—	—
	H	876a	6,129	4.9	..	LA, LD, RA	—
	H	877a	6,138	5.4	..	LA	LADB
	H	878a	6,147	5.3	RA	LA	—
	H	882a	6,183	5.4	LA	—	—
	H	883a	6,192	4.7	RA, RD, RI	LA	—
	H	885a	6,210	5.0	..	LA, RA	LMB
	H	889a	6,246	5.0	..	LA	—
	H	890a	6,255	4.9	LA	—	—
	H	892a	6,273	5.7	LC, RA	—	—
	H	892b	6,273	5.3	..	LA, RA	—
	H	897a	6,318	5.2	RA	—	—
	H	897b	6,318	4.5	LC	LA	—

TABLE 19.—*Data on dogs with lung tumors indicating type of tumor and lobe in which the tumor was found (cont.)*

Group		Day of death	Number of cigarettes	Age at death (years)	Lobes with bronchiolo-alveolar tumors Non-invasive	Invasive	Early squamous cell bronchial carcinoma
Group h (no filter)	h	606	3,769	4.6	LA	—	—
	h	626	3,928	4.4	..	LA, RI	—
	h	649	4,143	5.0	RI	LA, RA	—
	h	794	5,400	5.1	LA, RA	—	—

LA, left apical lobe; LC, left cardiac; LD left diaphragmatic; RA, right apical; RC, right cardiac; RI, right intermediate; RD, right diaphragmatic; LABB, left apical branch bronchus; LMB, left main bronchus.

For smoking dogs, the day of death indicates the number of days since start of smoking. The letter "a" or "b" follows the day of death of dogs sacrificed after day #875.

SOURCE: Auerbach, O, et al. (*11*).

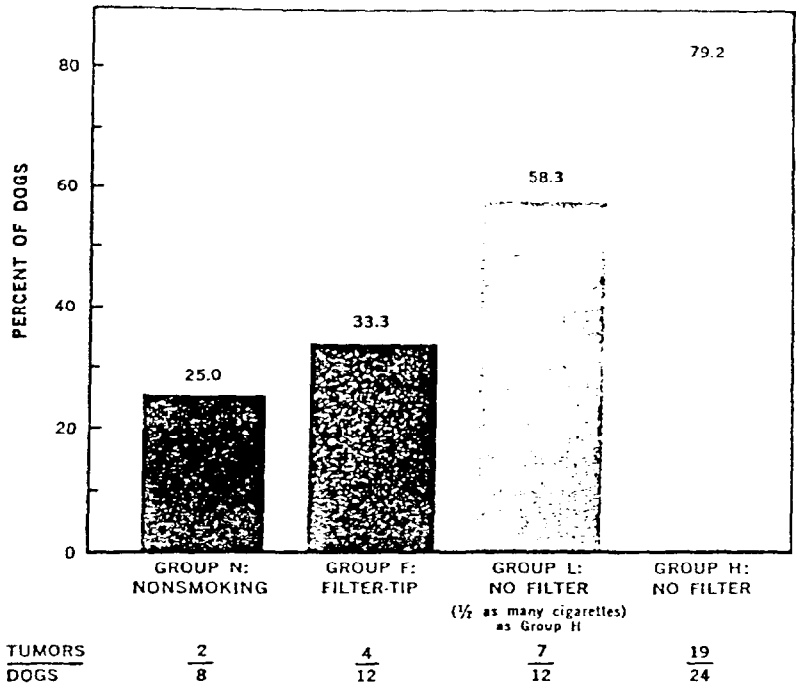

FIGURE 2.—Percent of smoking dogs with tumors.
SOURCE: Adapted from Auerbach, O., et al. (11).

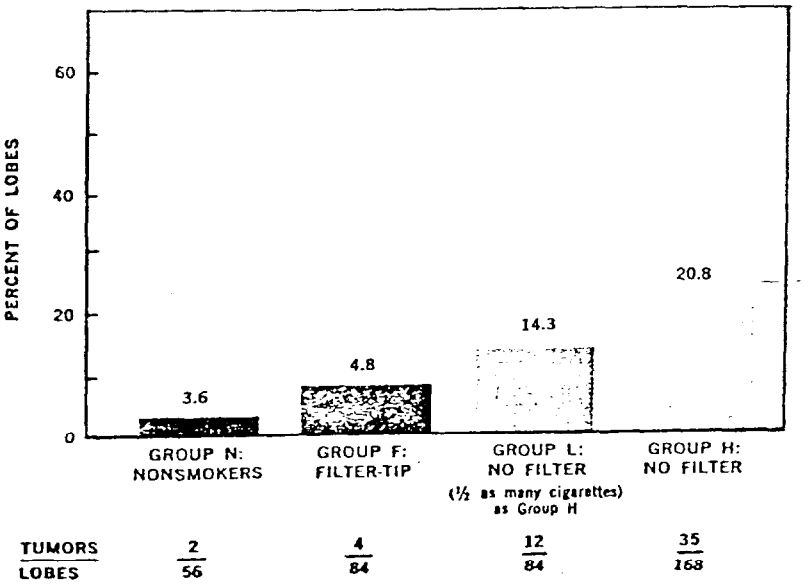

FIGURE 3.—Percent of lung lobes with tumors in smoking dogs.
SOURCE: Adapted from Auerbach, O., et al. (11).

cigarette smokers (*6*, *42*, *112*), but the magnitude of this relationship is not as great as that with squamous cell cancer in man.

Reduction in Tumorigenicity

The importance of reducing total particulate matter in cigarette smoke is reflected in the dose-dependent results of the Auerbach-Hammond study. A major objective of experimental tobacco carcinogenesis must be the reduction in the tumorigenicity of cigarette smoke and other tobacco products. In a recent article (*320*), Wynder and Hoffmann have reviewed the various methods applied to achieve this goal. Among these methods are the modification of the tobacco itself, the modification of the conditions of tobacco pyrolysis, the use of additives, and the use of filters. The use of filters should produce a reduction of particulate matter as well as of gas phase components.

Bross (*44*) studied 974 cases of lung cancer at Roswell Park Memorial Institute and concluded that smokers who switched to filter cigarettes showed a decreased risk of developing lung cancer. However, even after switching, heavy smokers were still found to have a mortality risk five times that of nonsmokers.

More recently, Wynder, et al. (*324*) reported on an interview study of 350 patients with histologically confirmed lung cancer and 552 age and sex-matched controls. They found that subjects who had switched from nonfilter to filter cigarettes ten or more years prior to the study incurred a lower relative risk of lung cancer at all consumption levels than that incurred by those who continued to smoke nonfilter cigarettes. The authors suggest that this difference in relative risk may be due to the lower "tar" content in filter cigarette smoke. Prospective studies concerning the effects of filter cigarette smoking are presently being conducted.

Apart from variations in "tar" exposure due to filtration, it appears that different patterns of smoking result in the inhalation of varied amounts of "tar." Graham, et al. (*103*) simulated different inhalation patterns with the use of an analytic smoking machine. He found that smoking a given number of puffs over a long period of time results in greater "tar" retrieval than smoking them over a short period. Also, he observed that taking most of the puffs at the end of the cigarette results in the highest retrieval while taking most at the beginning results in the smallest retrieval. Complementing these observations is the same author's case/control study (*102*) of 183 men with lung cancer and 161 men with diseases not related to tobacco smoking. He found that the lung cancer patients had significantly greater high "tar" yield cigarette smoking patterns than the controls. The risk of lung cancer was found to increase with the increase in mean number of puffs per

cigarette, the average length of time taken to smoke a cigarette (except in the highest number of puffs category), and the taking of more puffs at the end of the cigarette.

These findings, and those of the study of Auerbach, et al. (*11*), add further support to the dose-response relationship between lung cancer and total cigarette smoke condensate exposure.

Summary and Conclusions

1. Epidemiological evidence derived from a number of prospective and retrospective studies coupled with experimental and pathological evidence confirm the conclusion that cigarette smoking is the main cause of lung cancer in men. These studies reveal that the risk of developing lung cancer increases with the number of cigarettes smoked per day, the duration of smoking, and earlier initiation, and diminishes with cessation of smoking.

2. Cigarette smoking is a cause of lung cancer in women but accounts for a smaller proportion of cases than in men. The mortality rates for women who smoke, although significantly higher than for female nonsmokers, are lower than for men who smoke. This difference may be at least partially attributed to difference in exposure; such as, the use of fewer cigarettes per day, the use of filtered and low "tar" cigarettes, and lower levels of inhalation. Nevertheless, even when women are compared with men who apparently have similar levels of exposure to cigarette smoke, the mortality ratios appear to be lower in women.

3. The risk of developing lung cancer among pipe and/or cigar smokers is higher than for nonsmokers but significantly lower than for cigarette smokers.

4. The risk of developing lung cancer appears to be higher among smokers who smoke high "tar" cigarettes or smoke in such a manner as to produce higher levels of "tar" in the inhaled smoke.

5. Ex-cigarette smokers have significantly lower death rates for lung cancer than continuing smokers. There is evidence to support the view that cessation of smoking by large numbers of cigarette smokers would be followed by lower lung cancer death rates.

6. Increased death rates from lung cancer have been observed among urban populations when compared with populations from rural environments. The evidence concerning the role of air pollution in the etiology of lung cancer is presently inconclusive. Factors such as occupational and smoking habit differences may also contribute to the urban-rural difference observed. Detailed epidemiologic surveys have shown that the urban factor exerts a small influence compared to the overriding effect of cigarette smoking in the development of lung cancer.

7. Certain occupational exposures have been found to be associated with an increased risk of dying from lung cancer. Cigarette smoking interacts with these exposures in the pathogenesis of lung cancer so as to produce very much higher lung cancer death rates in those cigarette smokers who are also exposed to such substances.

8. Experimental studies on animals utilizing skin painting, tracheal instillation or implantation, and inhalation of cigarette smoke or its component compounds, have confirmed the presence of complete carcinogens as well as tumor initiators and promoters in tobacco smoke. Lung cancer has been found in dogs exposed to the inhalation of cigarette smoke over a period of more than two years.

CANCER OF THE LARYNX

Cancer of the larynx is a disease which predominantly affects males in the 55 to 70 year age group. In 1967, a total of 2,468 males and 329 females died of laryngeal cancer in the United States. With the development and application of more effective therapy during the past 30 years, the death rate for cancer of the larynx appears to be dropping slightly (*282, 289*); however, the incidence continues to rise. Figures from the Connecticut Cancer Registry (*88*) show that the age-adjusted incidence per 100,000 population of cancer of the larynx for males rose from 3.0 in 1950 to 5.6 in 1961.

EPIDEMIOLOGICAL STUDIES

A number of epidemiological studies have investigated the relationship between smoking habits and the development of cancer of the larynx. The major prospective studies, as outlined in table 20, show that smokers of cigarettes run an approximately six-to-tenfold risk of dying from this form of cancer as compared to nonsmokers. Smokers of pipes and cigars incur a three-to-sevenfold risk. The retrospective studies listed in table A21 uniformly show fewer nonsmokers and more smokers among cases with cancer of the larynx than among matched controls. Table A22 summarizes the relative risk ratios derived from the retrospective studies. The wide variation is due to a number of factors, including type of population and interview technique. But, in general, the magnitude of most of these ratios is of the same order as in the prospective studies.

Wynder, et al. (*312*) have distinguished between cancer of the intrinsic and extrinsic larynx. Tumors arising on the vocal cords are classified as intrinsic and constitute approximately 70 percent of the lesions. The extrinsic larynx is composed of those sections of the larynx excluding the vocal cords and may also be referred to as

TABLE 20.—*Laryngeal cancer 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 laryngeal cancer deaths	Cigarettes/day	Pipes, cigars	Comments
Hammond and Horn, 1958, U.S.A. (*120*).	187,783 white males 50–69 years of age in 9 states.	Questionnaire and follow-up of death certificate.	3½	24 SM ..24 NS .. 0	Cigarette smokers 17/24.	*Cigar* 3/24 *Mixed* 4/24	Data referring to mortality ratio included cancer of esophagus and mouth.
Doll and Hill, 1964, Great Britain (*74*).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	16 SM ..16 NS .. 0	*All smokers by amount in grams* NS ..... 1–14 ..... 1.00 15–24 ..... 1.00 >25 ..... 7.50	*Pipe and cigar*† NS .... 1.00 SM 5.00	† Includes data on ex-smokers of pipes and cigars. No NS died of laryngeo-tracheal cancer, therefore 1–14 gram SM set as 1.00 standard. Data combine laryngeal and tracheal carcinoma.
Kahn (Dorn), 1966, U.S.A. (*139*).	U.S. male veterans, 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	54 SM ..51 NS .. 3	NS ..... 1.00 (3) 1–9 ..... 3.27 (1) 10–20 ..... 8.45 (10) 21–39 ..... 13.62 (11) >39 ..... 18.85 (3) All 9.95 (25)	*Pipe* NS .... 1.00 (3) SM ....10.33 (6) *Pipe and cigar* NS .... 1.00 (3) SM 7.28 (11)	Refers to current cigarette smokers only.
Hammond, 1966, U.S.A. (*118*).	440,558 males 562,671 females 35–84 years of age in 25 states.	Interviews by ACS volunteers.	4	57 SM ..54 NS .. 3	NS ..... 1.00 (3) SM (age 45–64) .. 6.09 (32) SM (age 65–79) .. 8.99 (18)	*Pipe and cigar* NS .... 1.00 (3) SM 8.37 (4)	Male data only. Pipe and cigar data refer to males 55–84 years of age.

TABLE 20.—*Laryngeal cancer mortality ratios (cont.)*

(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 laryngeal cancer deaths	Cigarettes/day	Pipes, cigars	Comments
Weir and Dunn, 1970, U.S.A. (306).	68,153 males in various occupations in California.	Questionnaire and follow-up of death certificate.	5-8	11 SM ..11 NS .. 0	NS ..... — ±10 ..... 1.00 ±20 ..... 5.99 >30 ..... 5.84		No nonsmokers died of laryngeal carcinoma, therefore ±10 smoker set as 1.00 standard. NS includes pipe and cigar smokers. SM includes ex-smokers.

[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.

the hypopharynx. These authors noted that the percentage of heavy smokers among the patients with cancer of both the extrinsic and intrinsic larynx was significantly greater than that among controls. However, it is of interest that the excess risk of laryngeal cancer among cigar and pipe smokers in this study could be attributed to the extrinsic laryngeal group.

As in studies of oral cancer, it appears that alcohol consumption should also be taken into account in studies of laryngeal cancer. Wynder, et al. (*312*) reported a significantly increased risk of extrinsic cancer among those with alcohol intake above 7 ounces of whiskey per day. With less than this amount, no increased risk was evident. Schwartz, et al. (*248*), noted no effect in relation to alcohol intake. Further research into the interaction of these two variables is necessary.

Pathological Study

Auerbach, et al. (*9*) studied histological changes in the larynges of 942 men, age 21 to 95, who were autopsied at a single hospital between 1964 and 1967. Cases of primary cancer of the larynx were excluded from the study. Smoking histories for all cases were obtained from family members of the deceased by trained interviewers. The randomized histological sections were graded by one observer. Tables A23 and A24 summarize the findings in the true vocal cord. Of the men who never smoked, 75 percent had no cells with atypical nuclei, only 4.5 percent had sections with areas containing 60 to 69 percent of cells with atypical nuclei, and none had a higher percentage. The 116 ex-smokers had laryngeal histology similar to that of the nonsmokers, as far as atypical nuclei were concerned. However, disintegrating nuclei were found in 40.5 percent of the ex-cigarette smokers and in only 0.4 percent of the remaining cases. Only one of the 94 cigar and/or pipe smokers had no atypical cells. Three had carcinoma *in situ*, and one case had a section showing early invasive primary carcinoma.

The highest percentage of atypical cells was found among the cigarette smokers. The proportion of cases with a high degree of cellular change increased with increased daily smoking. None of the pack-or-more-a-day smokers was free of atypical nuclei in the laryngeal epithelium. Of those who smoked two or more packs per day, 85 percent had lesions with 60 percent or more atypical cells as compared to 4 percent of the nonsmokers. Between 10 and 18 percent of the cigarette smokers had areas of carcinoma *in situ*, and 4 of the 644 cases showed early microscopic invasion. The thickness of the basal level of the true vocal cord was also directly related to the amount smoked.

Experimental Study

Dontenwill (*76*) has recently reported the development of an effective and practicable method by which small rodents (hamsters, rats, mice) can be exposed to long-term passive inhalation of cigarette smoke in a manner which circumvents the fatal effects of acute toxicity which ruined earlier attempts but allows for a dosage of smoke great enough to induce the development of chronic pathological changes. The Syrian Golden hamster was found to be the most suitable species for such inhalation experiments for several reasons: its resistance to pulmonary infections, its resistance to the effects of nicotine as compared to that of rats or certain strains of mice, and, especially, its susceptibility to develop tracheobronchial cancers after treatment with carcinogens, in contrast to its almost total freedom from the spontaneous development of these tumors.

Dontenwill demonstrated that the concentration of deposited cigarette smoke was greatest in the hamster's larynx as compared to the other portions of the exposed respiratory tract (table 25), and that the laryngeal epithelium was the tissue which underwent the greatest smoke-induced histological changes.

In studying the changes in the larynx, the author differentiated five stages of epithelial change, using as his reference the Atlas of Tumor Pathology of the Armed Forces Institute of Pathology (*5*). Table 26, quoted by Dontenwill, describes the five types of change. They range from benign, such as epithelial hyperplasia, to premalignant, exemplified by pseudoepitheliomatous leukoplakia.

The results of the inhalation experiment are presented in figure 4 in which a dosage-related increase in the severity of the epithelial changes is represented in graphic form. The author also reported, and depicted with photomicrographs, the finding of an early invasive squamous cell carcinoma. This form of cancer is the predominant type involving the human larynx.

Summary and Conclusions

1. Epidemiological, experimental, and pathological studies support the conclusion that cigarette smoking is a significant factor in the causation of cancer of the larynx. The risk of developing laryngeal cancer among cigarette smokers as well as pipe and/or cigar smokers is significantly higher than among nonsmokers. The magnitude of the risk for pipe and cigar smokers is about the same order as that for cigarette smokers, or possibly slightly lower.

2. Experimental exposure to the passive inhalation of cigarette smoke has been observed to produce premalignant and malignant changes in the larynx of hamsters.

TABLE 25.—*Deposition of ^{14}C-labeled smoke particles in particular regions of the respiratory tract*[1]

Organ	Traced radio-activity (nCi)	Organ	Estimated radio-activity (nCi)	Deposition of particles (%)	Proportional area of the respiratory tract	Traced deposition in relation to the proportional area
Head and palate ...	6.11	Head, palate	5.5	37.4		
Tongue	0.41	Oral cavity in total.	1.6	10.9		
Larynx	0.39				0.1–0.3	X561–187
Trachea	0.26		7.6 (traced)	51.7	0.6	X62.3
Lungs	6.95				1000	X1
Total	14.12		[2]14.7	100.0		

[1] Cigarettes labeled with ^{14}C-1-n-hexadecan; data represent mean values from 10 animals, calculated from surface distribution in the head.

[2] The value of 14.7 contains 0.58 nanocuries as estimated from quantity of deposition in the nontraced oral cavity regions (calculated as to proportional area).

SOURCE: Dontenwill, W. (*76*).

TABLE 26.—*Classification of the five registered stages of epithelial changes at the larynx*[1, 2]

Stage	Acanthosis (thickening of stratum spinosum multicellular layer)	Hyperkeratosis increased cornification (stratum corneum)	Parakeratosis (incomplete cornification of nuclei in the stratum corneum)	Dyskeratosis (premature atypical cornification changes in the nucleus proliferation of the basal layer)	Mitosis
1. Pachydermia (epithelial hyperplasia)	+	+	†	†	†
2. Leucoplakia	+	+	‡	‡	‡
3. Verrucous leucoplakia	+	+	+	‡	‡
4. Papillomatous leucoplakia	+	†	†	++	‡
5. Pseudoepitheliomatous leucoplakia	+	+	+	+++	+

[1] Symbols: † = negative; ‡ = minimal; + = weak; ++ = medium; +++ = strong.
[2] From Atlas of Tumor Pathology of the Armed Forces Institute of Pathology.
SOURCE: Adapted from Dontenwill, W. (*76*).

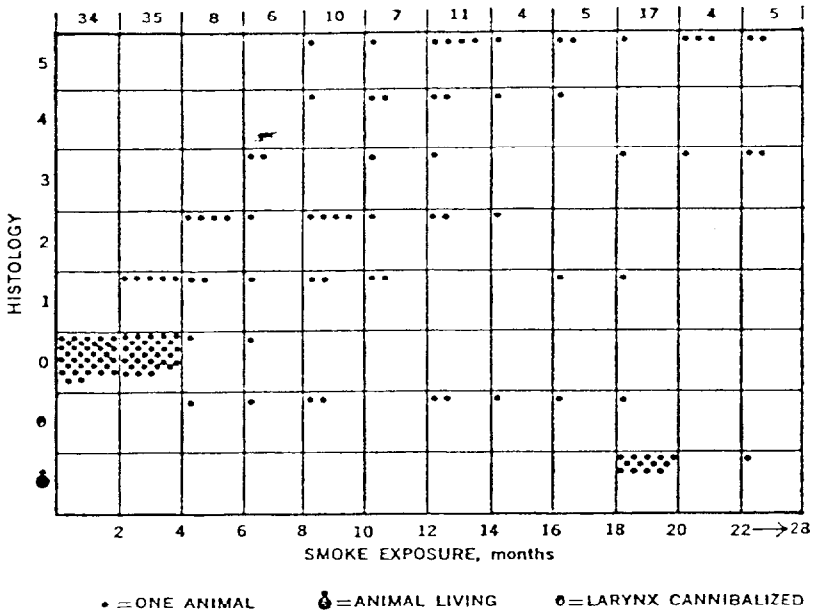

FIGURE 4.—Effects of chronic cigarette smoke inhalation on the hamster larynx. Review of the results of the inhalation experiments: number of smoke-exposed animals with and without changes in the larynx, duration of smoke exposure, and number of animals still alive.
SOURCE: Dontenwill, W. (*76*).

ORAL CANCER

The cancers included in this category are those of the lips, tongue, floor of the mouth, hard and soft palate, gingiva, alveolar mucosa, buccal mucosa, and oropharyns. It is estimated that 15,000 of these cancers will be diagnosed in the United States in 1970, accounting for about 2.5 percent of the estimated 600,000 malignant neoplasms reported (*289*). A variety of histological types of malignant neoplasms can affect these tissues, but squamous cell carcinoma is by far the predominant type, accounting for about 90 percent of the cancers.

The incidence of and mortality from oral cancers has remained steady over the past 20 to 30 years. The Connecticut Cancer Registry (*88*), which is a fairly reliable index of incidence, noted that the incidence among males remained between 15.8 and 16.3 per 100,000 population during the years from 1950–1961. Examination of mortality rates over the past 20 to 30 years (*282, 289*) reveals a similar constancy.

The apparent lack of change in mortality from oral cancer in

contrast to the sharp increase that took place in lung cancer rates in those years is probably due to several of the following factors. First, pipe and cigar smoking are both significantly related to cancer of the oral cavity, and the increase in cigarette smoking among men, noted between 1920 and 1955, has been, to a large degree, accompanied by corresponding reductions in the use of pipes and cigars. Second, aside from the various changes which the International Classification of Diseases (ICD) had undergone during that period, the diseases discussed above are recorded in ICD Codes 140–148 which include some neoplasms not found to be related to the use of tobacco. The various sites of cancer themselves do not contribute equally to the overall rate and are subject to widely different cure rates, so that their contributions to the total incidence rate is different from their contribution to the overall mortality rate from oral cancer. Although more than 20,000 cancers of the oral cavity were estimated as newly diagnosed in 1967, the total number of individuals recorded as dying from oral cancer during that year was only 6,718 (*289*).

Oral cancer occurs predominantly in people of the middle and older age groups. More than 90 percent of all oral cancers occur in persons over age 45, with the average age at time of diagnosis approximating 60. Although the majority of oral cancers occur in men, there is recent evidence that the ratio of males affected to females affected is decreasing (*257*).

Epidemiological Studies

The use of tobacco in various forms has been associated with the development of cancer of the oral cavity and pharynx. The studies in this area of concern are truly international, many having been carried out in Asian nations as well as in the West.

The major prospective epidemiological studies have found increased rates of these cancers for cigarette smokers as well as for pipe and cigar smokers (see table 27). Pipe smoking, per se, has long been recognized as a cause of lip cancer (*291*). The methodology and results of the numerous retrospective studies are summarized in tables A28 and A28a. These studies almost uniformly show significant relationships between the various forms of tobacco use and cancers of the oral cavity and pharynx.

Studies in Asian nations have examined the prevalence or incidence of premalignant change, such as oral leukoplakia, as well as that of cancer of the oral cavity. In many of these studies, forms of tobacco use not prevalent in Western countries have been investigated, including reverse smoking (in which the lighted end of the cigarette is kept in the mouth close to the palate) and the chewing

TABLE 27.—*Oral cancer mortality ratios—prospective studies*

(Actual number of deaths shown in parentheses)

SM = Smokers. NS = Nonsmokers.

Author year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths	Cigarettes	Pipes, cigars	Comments
Hammond and Horn, 1958, U.S.A. (*140*).	187,783 white males in 9 States 50–69 years of age.	Questionnaire and follow-up of death certificate.	3½	56 †SM ..51 NS .. 3	20/56	*Pipe* *Mixed* 5/56 21/56 *Cigar* 5/56	Data referring to mortality ratio do not include cancer of larynx and esophagus. † Excludes two occasional only smokers.
Doll and Hill, 1964, Great Britain (*74*).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	19 SM ..19 NS .. 0	*All smokers by amount in grams* NS ..... — 1–4 ..... 1.00 15–24 ..... 0.25 >25 ..... 5.25	*Pipe and cigar* NS ..... 1.00 SM 1.00	No NS died of oral cancer, therefore 1–14 gram smoker set as 1.00 standard.
Kahn (Dorn), 1966, U.S.A. (*139*).	U.S. male veterans, 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	61 SM ..50 NS ..11	NS ..... 1.00(11) †Cigs/day 1–9 .... 0.86 (1) 10–20 ..... 2.93(13) 21–39 ..... 7.34(20) >39 ..... 5.73 (3) All ..... 4.09(37)	*Pipe* NS ..... 1.00(11) SM ..... 3.12 (4) *Cigar* NS ..... 1.00(11) SM 4.11 (9)	Data do not include pharynx. † Refers to current cigarette smokers only.
Hammond, 1966, U.S.A. (*113*).	440,558 males 562,671 females 35–84 years of age in 25 States.	Interviews by ACS volunteers	4	95 SM ..88 NS .. 7	NS ..... 1.00 (7) SM (age 45–64) ... 0.00(63) SM (age 65–79) .. 2.03(25)	† Pipe and/or cigar. NS ..... 1.00 (7) SM ..... 4.04(15)	† Male data only. Pipe and cigar data refer to males 55–84 years of age.
Weir and Dunn, 1970, U.S.A. (*306*).	68,163 males in various occupations in California.	Questionnaire and follow-up of death certificate.	5–8	10	NS ..... 1.00 ±10 ..... 3.69 ±20 ..... 1.17 >30 ..... 5.52 All 2.70		SM includes ex-smokers. NS includes pipe and cigar smokers.

of "pan" or "Nass," which are mixtures of tobacco with either betel nut or lime ash, and other ingredients (*241, 255, 256*). Snuff dipping, a habit in which snuff is placed in the gum and retained there for prolonged periods, has also been associated with the development of oral cancer (*193, 210*), as has the chewing of tobacco (*124, 193, 241, 298*).

The risk of developing a second primary mouth or throat cancer, after the recognition of the first primary cancer, has been found to be greater in continuing smokers than in those who quit smoking. All of the patients studied by Moore (*190*) were asymptomatic for at least three years following the treatment of the first cancer. Of the 117 patients with adequate smoking histories, only 4 of 43 (9 percent) who quit smoking developed a new primary cancer. On the other hand, 27 of 74 (36 percent) who continued to smoke developed a second primary cancer.

However, a study by Castigliano (*53*) of patients treated for oral cancer did not show a greater risk of a second primary among continuing smokers. In this study, 5 of 26 (19 percent) of those patients who did not quit smoking developed a second primary cancer as compared to 9 of 51 (18 percent) of those who did quit. The rate of quitting smoking in the two studies is markedly different (36 percent in the Moore study and 62 percent in the Castigliano study). From the data presented in the two papers, it is not possible to evaluate the other significant ways in which the populations may have differed.

Keller (*140*) studied 408 males with histologically confirmed squamous cell cancer of the mouth or pharynx. This author dealt with the question of recurrent tumors in a somewhat different manner. The patients were observed for the development of a second or third primary cancer at an anatomically discrete site of the mouth and pharynx within a median period of three years after the first cancer. He found that a second or third cancer (termed a coexisting cancer) developed in 28 of the 408 cases. Among these 28 cases with 33 coexisting neoplasms, 21.7 percent were heavy smokers, but among their matched controls, there were no heavy smokers. Coexisting cancers were most commonly found on the soft palate, an anatomical site that is in direct contact with the mainstream of tobacco smoke.

More recently, Wynder, et al. (*315*) studied 63 male and 23 female patients with multiple primary cancers of the mouth and pharynx. They observed that heavy smoking prior to the development of the oral cancer was associated with a greater likelihood of developing a second primary. Also, continued smoking after the first primary was found to have a significant association with the occurrence of a second primary.

With or without smoking, use of alcohol appears to contribute to the development of oral cancer (*124, 140, 183, 297, 322*). In a study of male veterans, Keller (*140*) found that heavy smoking and heavy drinking were associated with cancer of the mouth and pharynx. No studies are presently available which determine the relative contributions and possible interactions of heavy smoking, heavy drinking, and concurrent nutritional deficiencies in the etiology of these cancers.

Experimental Studies

In 1964, the Advisory Committee to the Surgeon General on Smoking and Health (*291*) reported that cigarette smoke and cigarette smoke condensates had failed to produce cancer when applied to the oral cavity of mice and rabbits or to the palate of hamsters and that the oral mucosa appears to be resistant in general to cancer induction even when highly active carcinogens such as benzo-[a]pyrene are applied. Some of the difficulties in experimental design were attributed to the fact that mechanical factors, such as secretion of saliva, interfere with the retention of applied carcinogenic agents on the tissues of the oral cavity and pharynx. Positive results with certain carcinogens have, however, been obtained in the hamster cheek pouch, but it has also been pointed out that the cheek pouch lacks salivary glands and that its structure and function differ from those of the oral mucosa. The majority of these studies are outlined in table A29.

Although cigarette smoke condensate acts as a complete carcinogen on mouse skin, the work of several authors (*319*) supports the concept that cigarette smoke contains cancer promoters that may be of special importance, particularly in oral carcinogenesis. Elzay (*90*) has reported that whole cigarette smoke is a promoting agent for the hamster cheek pouch. More importantly, regarding the chewing of tobacco, Bock, et al. (*27,30*), Van Duuren, et al. (*294*), and Wynder and Hoffmann (*321*) have shown that unburned tobacco products contain tumor promoters that might contribute to the promoting activity of the smoke.

Roth, et al. (*226, 227*) have shown that the dye-binding capacity of the DNA of oral epithelial cells is significantly enhanced in cigarette smokers in contrast to nonsmokers, probably reflecting an increase in the DNA content of oral epithelial cells in smokers. Smokers had values of dye-binding capacity intermediate between nonsmokers and 21 patients with proven oral cancer. Those smokers who refrained from smoking for up to six months showed a significant decrease toward more normal values.

Summary and Conclusions

1. Epidemiological and experimental studies contribute to the conclusion that smoking is a significant factor in the development of cancer of the oral cavity and that pipe smoking, alone or in conjunction with other forms of tobacco use, is causally related to cancer of the lip.

2. Experimental studies suggest that tobacco extracts and tobacco smoke contain initiators and promoters of cancerous changes in the oral cavity.

CANCER OF THE ESOPHAGUS

Esophageal cancer accounted for 4,306 deaths among American males in 1967 and 1,321 deaths among females. The death rate from esophageal cancer has remained relatively constant since 1949.

Epidemiological Studies

The major prospective epidemiological studies (table 30) have indicated a significant relationship between smoking and esophageal cancer. Overall mortality ratios for male cigarette smokers range from 1.74 to 6.17. There are insufficient data concerning females for establishing firm conclusions.

A number of retrospective studies concerning the relationship of smoking and esophageal cancer are outlined in table A31 and A31a. Smokers incur risk ratios ranging from 1.3 to 6.6 when compared with nonsmokers.

As in studies of oral cancer, the effect of alcohol consumption must be taken into account in studies of esophageal cancer. Because a relationship between alcohol consumption and tobacco use is known to exist, Wynder and Bross (*310*) analyzed the association between tobacco consumption and esophageal cancer after adjusting for alcohol intake. They found that in the absence of alcohol consumption, there was no association between the use of tobacco and esophageal cancer but that in the presence of alcohol consumption, an increasing relative risk with increasing number of cigarettes smoked was apparent, as well as an association between cigar and pipe smoking and esophageal cancer.

More recently, Takano, et al. (*272*), in a retrospective study of 200 patients with esophageal carcinoma, found an increased risk with smoking which was magnified by increased alcohol consumption. Martinez (*183*) analyzed the association of tobacco usage and esophageal cancer after controlling for age, sex, and alcohol consumption. Increasing relative risks with increasing tobacco use

TABLE 30.—*Esophageal cancer mortality ratios—prospective studies*
(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 esophageal cancer deaths	Cigarettes/day	Pipes, cigars	Comments
Hammond and Horn, 1958, U.S.A. (*180*).	187,783 white males in 9 States 50–69 years of age.	Questionnaire and follow-up of death certificate.	3½	34 NS ... 1 SM ... 33	Cigarette smokers 15/33.	*Pipe* 2/33 *Cigar* 2/33 *Mixed* cigarette smokers 13/33	Data referring to mortality ratios included cancer of mouth and larynx.
Doll and Hill, 1964, Great Britain (*74*).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	29	*All smokers by amount in grams* NS ..... 1.00 1–14 .... 2.00 15–24 .... 3.50 >25 ..... 5.00 All 3.00	†*Pipe and cigar* NS .... 1.00 SM 2.00	†Includes ex-smokers of pipe and cigars.
Kahn (Dorn), 1966, U.S.A. (*139*).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	111 NS ... 11 SM ...100	NS ..... 1.00(11) †1–9 ..... 1.76 (2) 10–19 .... 4.71(18) 20–39 ....11.50(24) >25 ..... 7.65 (3) All ..... 6.17(47)	*Pipe* 1.09 (3) *Cigar* 5.33(12)	†Refers to cigarette smoking only.
Hammond, 1966, U.S.A. (*118*).	440,558 males 562,671 females 35–84 years of age in 25 States.	Interviews by ACS volunteers.	4	46 NS ... 6 SM ... 40	NS ..... 1.00 (6) SM (age 45–64) . 4.17(32) SM (age 65–79) . 1.74 (8)	*Pipe and Cigar* NS .... 1.00 SM .... 3.97(14)	

TABLE 30.—*Esophageal cancer mortality ratios—prospective studies (cont.)*

(Actual number of deaths shown in parentheses)

SM = Smokers, NS = Nonsmokers.

Author year, country, reference	Number and type of population	Data collection	Follow-up years			Comments
Hirayama, 1967, Japan (*185*).	265,118 male and female adults 40 years of age and older.	Trained PHS nurse interview and follow-up of death certificate.	1½	SM ... 21	NS ..... 1.00 ($p<0.01$) SM 2.47 (21)	Refers to all forms of smoking.
Weir and Dunn, 1970, U.S.A. (*306*).	68,163 males in various occupations in California.	Questionnaire and follow-up of death certificate.	5-8	32	NS ..... 1.00 ±10 ..... 1.27 ±20 ..... 1.69 >30 ..... 1.82 All 1.82	NS includes pipe and cigar smokers.

[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.

were noted. The consumption of very hot beverages was also found to be related to the development of esophageal cancer.

Pathological Study

Autopsy studies of smokers as compared with nonsmokers, specifically observing the pathological changes in esophageal tissue, have been performed by Auerbach, et al. (*15*). A microscopic study was made of 12,598 sections of esophageal autopsy tissue from 1,268 men who died from causes other than esophageal cancer. The findings were strikingly similar to the abnormalities generally accepted as representing premalignant tissue changes in the respiratory tract epithelium. Esophageal epithelial cells with atypical nuclei (having an irregular distribution of chromatin) were found far more frequently in cigarette smokers than in nonsmokers. Basal cell hyperplasia and hyperactive glands were also found more frequently in cigarette smokers than in nonsmokers. An increase in frequency with amount of cigarette smoking was noted for both epithelial cells with atypical nuclei and basal cell hyperplasia. Tables A32 and A33 summarize these findings.

Experimental Studies

Kuratsune, et al. (*156*) investigated the possibility that the carcinogens known to be present in tobacco smoke could penetrate the esophageal epithelium more readily if dissolved in aqueous ethanol. Mice were exposed to several compounds by esophageal intubation. Tissues were then removed and studied by fluorescence microscopy. Deeper penetration and a different distribution were found when B[a]P was dissolved in aqueous ethanol as compared to B[a]P in olive oil. It was also found that benzo[a]anthracene and fluoranthene dissolved in ethanol solution or aqueous caffeine solution could penetrate the epithelium of the esophagus.

Horie, et al. (*132*) reported on the development of 10 papillomas and one squamous cell carcinoma of the esophagus in a group of 63 mice periodically forced to drink a solution of benzo[a]pyrene dissolved in diluted ethanol. Twenty-six papillomas and one squamous cell carcinoma also developed in a group of 63 mice to which 4-nitroquinoline 1-oxide was administered in the same way. None of the 67 control animals given only diluted ethanol developed neoplasms.

Several other authors have reported nitrosamine-induced esophageal cancer in experimental animals (*56, 79, 80, 81*). As noted above, the presence of nitrosamines in cigarette smoke is still a subject of debate.

Summary and Conclusions

1. Epidemiological studies have demonstrated that cigarette smoking is associated with the development of cancer of the esophagus. The risk of developing esophageal cancer among pipe and/or cigar smokers is greater than that for nonsmokers and of about the same order of magnitude as for cigarette smokers, or perhaps slightly lower.

2. Epidemiological studies have also indicated an association between esophageal cancer and alcohol consumption and tthat alcohol consumption may interact with cigarette smoking. This combination of exposures is associated with especially high rates of cancer of the esophagus.

CANCER OF THE URINARY BLADDER AND KIDNEY

Epidemiological Studies (Bladder)

Cancer of the urinary bladder accounted for 6,019 deaths among American males and 2,743 deaths among American females in 1967 (*289*). Incidence rates have increased from 1949 to 1962 (*88*), but the death rates from bladder cancer have remained relatively stable during that period. Improvements in early diagnosis and therapy may have masked the increasing incidence of this disease.

A number of epidemiological studies have indicated that smokers have an increased risk of contracting or of dying from bladder cancer (see tables 34 and A35). Certain of these studies include kidney cancer mortality in the results. The major prospective studies, with the exception of that of British physicians, have shown bladder cancer mortality ratios among cigarette smokers ranging from 1.40 to 2.89. Smokers of more than 1 pack per day were shown to incur ratios of 3.42 to 5.41. The study by Doll and Hill (*74, 75*) of British physicians, on the other hand, reports death rates for smokers to be lower than those of nonsmokers based on 38 bladder cancer deaths. The mortality ratios for pipe or cigar smokers are substantially lower than those among cigarette smokers. Pipe smokers were shown by both Hammond and Horn (*120*) and Kahn (*139*) to incur ratios approximating 1.20.

Retrospective studies (table A35a) have also shown an increased proportion of smokers among bladder cancer patients when compared with matched controls. Relative risk ratios for bladder cancer among smokers range from 1.0 to 7.3 among all smokers and up to 10.3 among heavy smokers of all types.

TABLE 34.—*Kidney and urinary bladder cancer—prospective studies—Mortality ratios*

(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	Cigarette/day	Pipe, cigar	Kidney	Bladder	Comments
Hammond and Horn, 1958, U.S.A. (*120*).	187,783 white males in 9 States.	Questionnaire and interview.	3½	287 SM .249 NS .. 38	NS .... 1.00(38) <10 ... 2.00(14) 10-20 .. 2.00(42) >20 ... 3.42(41)	*Pipe* NS ...1.00(38) SM ...1.17(21) *Cigar* NS ...1.00(38) SM ...1.06(19)			Data include patients dying of prostatic carcinoma. Data refer to microscopically proven carcinomas.
Doll and Hill, 1964, Great Britain (*74*).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	38		NS ...1.00 SM ...0.41		*All SM by amount in grams* NS ...1.00 1-14 ..0.59 15-24 ..0.65 >25 ...0.76 All 0.71	
Best, 1966, Canada (*21*).	Approximately 78,000 male Canadian veterans.	Questionnaire and follow-up of death certificate.	10	114	NS .... 1.00 <10 ... 1.33(29) 10-20 .. 1.44(57) >20 ... 1.43(15) All .... 1.40(10)	*Pipe* NS ...1.00 SM ...0.56(10) *Cigar* NS ...1.00 SM ...1.16 (3)			Refers to genitourinary cancers as a group.
Hammond, 1966, U.S.A. (*118*).	440,558 males 562,671 females 35-84 years of age in 25 States.	Interviews by ACS volunteers.	4	*Bladder* 138 SM .115 NS .. 23 *Kidney* 104 SM . 82 NS .. 22		*Cigarettes* NS .....1.00(22) SM (age 45-64) ...1.42(54) SM (age 65-79) ...1.57(28)	*Cigarettes* 1.00(23) 2.00(59) 2.96(56)	*Male data only.* Bladder includes other urinary tract cancers.	

TABLE 34.—*Kidney and urinary bladder cancer—prospective studies—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	Cigarette/day	Pipe, cigar	Kidney	Bladder	Comments
Kahn (Dorn), 1966, U.S.A. (*139*).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	*Bladder* 224 SM 172 NS 52 *Kidney* 141 SM 102 NS 39		NS 1.00 (39) Pipe 1.32 (6) Cigar 0.77 (6) Cigarettes/day: 1–9 0.97 (4) 10–19 1.34 (21) 20–39 1.68 (10) >39 2.76 (5) All 1.46 (46)		1.00 (62) 1.20 (8) 0.94 (10) 1.10 (6) 1.03 (37) 3.20 (34) 2.62 (5) 2.15 (82)	Bladder includes other urinary tract cancers.
Hirayama, 1967, Japan (*125*).	265,118 male and female adults 40 years of age and older.	Trained PHS nurse interview and follow-up of death certificate.	1½	SM 6	NS 1.00 SM 10.00 (6)				Bladder cancer only. Refers to all forms of smoking.
Weir and Dunn, 1970, U.S.A. (*306*).	68,153 males in various occupations in California.	Questionnaire and follow-up of death certificate.	6–8	*Bladder* 27 *Kidney* 27			NS 1.00 ±10 0.86 ±20 3.30 >30 2.57 All 2.46	NS 1.00 ±10 1.52 ±20 2.81 >30 5.41 All 2.89	SM include ex-smokers. NS include pipe and cigar smokers.

[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.

Epidemiological Studies (Kidney)

A total of 5,894 Americans died of cancer of the kidney during 1967. A relationship between smoking and this type of cancer has been suggested by several epidemiological studies. The three major studies which separately examine the relationship of kidney cancer to smoking (table 34), namely those of Hammond (*118*), Kahn (*139*), and Weir and Dunn (*306*), have shown mortality ratios for all cigarette smokers to range from 1.42 to 2.46. Retrospective studies by Bennington, et al. (*18, 19*) have indicated a significant association between all forms of smoking and renal adenoma and adenocarcinoma.

Experimental Studies

Numerous experiments have been undertaken by many investigators to elucidate the relationship of tobacco smoking to bladder carcinogenesis. The two areas of major concern have centered upon the presence of a known bladder carcinogen, beta naphthylamine, in cigarette smoke and the presence of abnormal tryptophan metabolism in patients with bladder cancer.

By virtue of data gathered concerning industrial exposure of workers, beta naphthylamine has long been known as a bladder carcinogen. Complementing such data was the work of Hueper, et al. (*136*) who subjected mongrel dogs to daily subcutaneous injections and oral administration of commercial beta naphthylamine. Thirteen of the 16 animals developed bladder papillomas and carcinomas of the bladder. Saffiotti, et al. (*236*) fed hamsters a diet containing up to 1.0 percent beta naphthylamine and observed that 18 of 39 animals developed bladder tumors, almost all typical transitional cell carcinomas. More recently, Conzelman, et al. (*59*) administered beta naphthylamine to 24 rhesus monkeys for more than 30 months. Transitional cell carcinomas of the urinary bladder were induced in 9 of the animals, and a dose-response relationship was apparent.

Pailer, et al. (*207*) and Miller and Stedman (*185*) failed to find this amine in cigarette smoke. However, more recently, Hoffmann, et al. (*127*) identified it in cigarette smoke. The authors, noting the minute quantity present in each cigarette (2.2×10^{-9}g), hesitated to attach a biological significance to the finding.

Of more recent interest have been the metabolites of tryptophan present in certain patients with bladder cancer. A number of normal and abnormal metabolites of tryptophan have been found to be carcinogenic when tested by implantation in the bladders of mice. These include 3-hydroxykynurenine (OHKy), 3-hydroxyanthranilic

acid (OHA), 3-hydroxy-2-amino-acetophenone (all orthoaminophenols), the 8-methyl ether of xanthurenic acid (CHXa), xanthurenic acid (Xa), L-kynurenine (Ky), quinaldic acid, and 3-methoxyanthranilic acid (3CHOA) (*2, 36, 37, 39, 47, 48*). OHKy and OHA are frequently present in human urine, as is kynurenic acid (KyA).

Certain investigators have concentrated their attention on the presence of abnormal tryptophan metabolites and increased amounts of normal tryptophan metabolites in the urine of patients with bladder cancer as compared with selected controls (*1, 40, 46, 97, 148, 214, 243, 329*). These authors have observed the increased excretion of Ky, KyA, OHKy, anthranilic acid, OHA, and acetylkynurenine in such patients. Yoshida, et al. (*329*), in a recent study concerning the relationship between tryptophan metabolism and heterotopic recurrences of human urinary bladder tumors, reported that those patients with recurrences showed abnormal metabolite excretion more often than those without recurrences.

The relationship of smoking to these biochemical findings is presently uncertain. Kerr, et al. (*143*), in 30 experiments on 3 smokers and 3 nonsmokers who were given large doses of tryptophan, found that smoking increased the urinary excretion of OHKy and OHA and decreased that of N'methylnicotinamide (an end product of tryptophan metabolism). Kerr concluded that smoking interferes with the normal metabolism of tryptophan. Recently, Brown, et al. (*45*) studied 15 adults under smoking and abstinence conditions and found that except for the basal excretion of acetylkynurenine, tryptophan metabolite excretion did not change with smoking or cessation. The authors also compared 13 nonsmokers and 17 regular cigarette smokers under basal and tryptophan-loaded conditions. No differences were observed in the excretion of the measured tryptophan metabolites. However, due to its instability, OHA was not measured. The authors concluded that the relationship of smoking to urinary bladder cancer was probably not via its effect on the kynurenine pathway of tryptophan metabolism.

Another experimental approach to the relationship of smoking and urinary bladder cancer is reflected in the work of Schlegel, et al. (*244, 245*). The authors observed an elevated concentration of certain ortho-aminophenols in the urine of bladder cancer patients and cigarette smokers, when compared with nonsmokers (*244*). More recently (*245*), the same group compared the chemiluminescence of the urines of smokers, nonsmokers, and bladder tumor patients. They noted that nonsmokers showed the lowest level of luminescence (which they relate to the presence of aromatic hydrocarbons) and the bladder tumor patients the highest level. The normal cigarette smokers' level was found to be intermediate.

TABLE 36.—*Pancreatic cancer mortality ratios—prospective studies*

(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	Pipes, cigars	Comments
Best, 1966, Canada (*21*).	Approximately 78,000 male Canadian veterans.	Questionnaire and follow-up of death certificate.	6	SM ... 35	*Current (cigarettes only)* NS ..... 1.00 <10 .... 1.40 (5) 10-20 ... 1.00 (16) >20 .... 2.37 (7)	*Pipes* NS ..1.00 SM ..2.60 (6) *Cigars* NS ..1.00 SM ..2.63 (1)	
Hammond 1966 U.S.A. (*118*).	440,558 males 562,671 females 35-84 years of age in 25 States.	Interviews by ACS volunteers.	4	262 SM ...233 NS ... 29	NS ..... 1.00 (29) SM (age 45-64) 2.69 (168) SM (age 65-79) 2.17 (75)		Male data only.
Kahn (Dorn) 1966 U.S.A. (*139*).	U.S. male veterans, 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	344 †SM ...256 NS ... 88	NS ..... 1.00 (88) 1-9 .... 0.87 (8) 10-20 ... 1.93 (65) 21-39 ... 2.18 (43) >39 .... 1.87 (7) All 1.84 (125)	*Pipes* NS ..1.00 (88) SM ..0.74 (8) *Cigars* NS ..1.00 (88) SM ..1.52 (27) *Both* NS ..1.00 (88) SM ..0.93 (13)	† Refers to current smokers of all types.
Hirayama, 1967, Japan (*125*).	265,118 male and female adults 40 years of age and older.	Trained PHS nurse interview and follow-up of death certificate.	1½	SM ... 14	NS ..... 1.00 SM .....15.56 (14) } (p<0.01)		
Weir and Dunn, 1970, U.S.A. (*206*).	68,153 males in various occupations in California.	Questionnaire and follow-up of death certificate.	5-8	SM ... 71	NS ..... 1.00 ±10 .... 2.94 ±20 .... 2.45 >30 .... 1.44 All 2.43		SM includes ex-smokers. NS includes pipe and cigar smokers.

[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.

At present, no definite conclusions can be drawn concerning the interrelationships of bladder cancer, abnormal tryptophan metabolism, and tobacco smoking. Further study is required in this and the other areas of bladder cancer pathophysiology.

Summary and Conclusions

1. Epidemiological studies have demonstrated an association of cigarette smoking with cancer of the urinary bladder among men. The association of tobacco usage and cancer of the kidney is less clear-cut.
2. Clinical and pathological studies have suggested that tobacco smoking may be related to alterations in the metabolism of tryptophan and may in this way contribute to the development of urinary tract cancer.

CANCER OF THE PANCREAS

Several prospective epidemiologic studies have suggested a relationship between cigarette smoking and cancer of the pancreas (table 36). A retrospective study of 465 cases of pancreatic cancer by Ishii, et al. (*137*) has shown a dose-related increased risk of pancreatic cancer in association with smoking. Analysis of dietary data revealed that the relative risk for pancreatic cancer from smoking was considerably greater than from dietary factors.

No experimental studies relating to this question have been reported.

Summary and Conclusions

Epidemiological studies have suggested an association between cigarette smoking and cancer of the pancreas. The significance of the relationship is not clear at this time.

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APPENDIX TABLES

TABLE A3.—*Outline of methods used in retrospective studies of smoking in relation to lung cancer*

Author, year, country, reference	Sex of cases	Number of persons and method of selection		Collection of data
		Cases	Controls	
Müller 1939, Germany (*196*).	M	86 lung cancer decedents	86 healthy men of the same age	Cases: Questionnaire sent to relatives of deceased. Controls: Not stated.
Schairer and Schöniger, 1943, Germany (*242*).	M	93 cancer decedents autopsied (average age 53.9).	270 men aged 53 and 54	Cases: Questionnaire sent to next of kin. Controls: Questionnaire sent to 700.
Potter and Tully, 1945, U.S.A. (*212*).	M	43 male patients over 40 years of age.	1,847 patients of same group with diagnoses other than cancer.	Cases and controls interviewed in clinics.
Wassink, 1948, Netherlands (*304*).	M	134 male clinic patients with lung cancer.	100 normal men of same age groups as cases.	Cases: Interviewed in clinic. Controls: Not stated.
Schrek et al., 1950, U.S.A. (*246*).	M	82 male lung cancer cases among 5,003 patients recorded, 1941–48.	522 miscellaneous tumors other than lung, larynx, pharynx, or lip.	Smoking habits recorded during routine hospital interview.
Mills and Porter, 1950, U.S.A. (*186*).	M	444 respiratory cancer decedents.	430 sample of residents matched by age in Columbus, Ohio, from census tracts stratified by degree of air pollution.	Cases: Relatives queried by mail questionnaire or personal visit. Controls: House-to-house interviews.

TABLE A3.—*Outline of methods used in retrospective studies of smoking in relation to lung cancer (cont.)*

Author, year, country, reference	Sex of cases	Number of persons and method of selection		Collection of data
		Cases	Controls	
Levin et al., 1950, U.S.A. (*169*).	M	236 cancer hospital patients with diagnosed lung cancer.	481 patients in same hospital with nonmalignant diagnoses.	Cases and Controls: Routine clinical history taken *before diagnosis*.
Wynder and Graham, 1950, U.S.A. (*316*).	M-F	605 hospital and private lung cancer patients in many cities.	780 patients of several hospitals with diagnoses other than lung cancer.	Nearly all data by personal interview; a few cases by questionnaire; a few from intimate acquaintances. Some interviews with knowledge or presumption of diagnosis, some with *none*. 595 diagnosed by tissue examination, nine by sputum, and one by pleural fluid examination.
McConnell et al., 1952, England, (*180*).	M-F	100 lung cancer patients, unselected, in 3 hospitals in Liverpool area.	200 inpatients of *same* hospitals, matched by age and sex, without cancer.	Personal interviews by the authors of both cases and controls.
Doll and Hill, 1952, Great Britain (*79*).	M-F	1,465 patients with lung cancer in hospitals of several cities.	1,465 patients in same hospitals, matched by sex and age group; some with cancer of other sites, some without cancer.	Personal interviews of cases and controls by almoners.
Sadowsky et al., 1953, U.S.A. (*232*).	M	477 patients with lung cancer in hospitals in 4 states.	615 patients in same hospitals with illnesses other than cancer.	Personal questioning by trained interviewers.

TABLE A3.—*Outline of methods used in retrospective studies of smoking in relation to lung cancer (cont.)*

Author, year, country, reference	Sex of cases	Number of persons and method of selection		Collection of data
		Cases	Controls	
Wynder and Cornfield, 1953, U.S.A. (*314*).	M	63 physicians reported in AMA Journal as dying of cancer of the lung.	133 physicians of same group dying of cancer of certain other sites.	Mail questionnaire to estates of decedents.
Koulumies, 1953, Finland (*151*).	M–F	812 lung cancer patients diagnosed at one hospital.	300 male outpatients of same hospital over 40 years of age.	Cases and controls questioned about smoking habits when taking case histories. 361 diagnoses confirmed histologically; 494 diagnoses confirmed by clinical, X-ray, and operative data.
Lickint, 1953, Germany (*170*).	M–F	246 lung cancer patients in a number of hospitals and clinics.	2,002 sample of persons without cancer living in the same area and of the same sex and age range as cases.	Personal interviews by staff members of cooperating hospitals and clinics.
Breslow et al., 1954, U.S.A. (*42*).	M–F	518 lung cancer patients in 11 California hospitals.	518 patients admitted to same hospitals about the same time, for conditions other than cancer or chest disease, matched for race, sex, and age group.	Cases and controls questioned by trained interviewers, each matched pair by the same person.
Watson and Conte, 1954, U.S.A. (*305*).	M–F	301 patients at Memorial Hospital with lung cancer.	468 patients of same clinic during same period with diagnoses other than lung cancer.	The 769 consecutive patients of case and control groups were questioned by the same trained interviewer. Control group includes patients with oral and esophageal cancer and bronchitis.
Gsell, 1954, Switzerland (*107*).	M	135 men with diagnosis of bronchial carcinoma.	135 similar hospital patients with diagnoses other than lung cancer, and of the same age.	Personal interviews, all by the same person.

TABLE A3.—*Outline of methods used in retrospective studies of smoking in relation to lung cancer (cont.)*

Author, year, country, reference	Sex of cases	Number of persons and method of selection		Collection of data
		Cases	Controls	
Randig, 1954, Germany (*218*).	M-F	448 lung cancer patients in a number of West Berlin hospitals.	512 patients with other diagnoses, matched for age.	Controls were interviewed at about the same time as the cases, each case-control pair by the same physician.
Wynder et al., 1956, U.S.A. (*311*).	F	105 patients with lung cancer in several New York City hospitals.	1,301 patients at Memorial Center with tumors of sites other than respiratory or upper alimentary.	Cases: Personal interview or questionnaire mailed to close relatives or friends. Controls: Personal interview.
Segi et al., 1957, Japan (*250*).	M-F	207 patients with lung cancer in 33 hospitals in all parts of the country.	5,536 patients free of cancer in 420 local health centers, selected to approximate the sex and age distributions of cases.	Cases and controls by personal interview using long questionnaire on occupational and medical history and living habits.
Mills and Porter, 1957, U.S.A. (*187*).	M-F	578 residents of defined areas dying of respiratory cancer.	3,310 population sample approximately proportional to cases as regards areas of residence, and 10 years or more in the area.	Cases: From death certificates, hospital records, and close relatives or friends. Controls: Personal home visits or telephone calls, usually interviewing housewife.
Stocks, 1957, England (*263*).	M-F	2,356 patients suffering from or dying with lung cancer within certain areas.	2,362 unselected patients of the same area admitted for conditions other than cancer.	Cases: Histories taken at the hospital from relatives by health visitors. Controls: Personal interview in hospital.
Schwartz and Denoix, 1957, France (*247*).	M	602 patients with bronchopulmonary cancer in hospitals.	1,204 patients (3 groups) in same hospitals with other cancer, with nonmalignant illness, and accident cases, matched by age group.	Personal interviews in the hospital; cases and controls at about the same time by the same interviewer.

TABLE A3.—*Outline of methods used in retrospective studies of smoking in relation to lung cancer (cont.)*

Author, year, country, reference	Sex of cases	Number of persons and method of selection		Collection of data
		Cases	Controls	
Haenszel and Shimkin, 1968, U.S.A. (*113*).	F	188 lung cancer patients available for interview in 20 hospitals.	339 patients in same hospital and service at same time, next older and next younger than each case.	Personal interviews by resident, medical social worker, or clinic secretary.
Lombard and Snegireff, 1969, U.S.A. (*176*).	M	500 men dying of lung cancer, microscopically confirmed.	4,238 controls in 7 groups including volunteers, hospital and clinic patients, random population sample, and house-to-house survey samples.	Personal interviews by trained workers.
Pernu, 1960, Finland (*211*).	M-F	1,606 respiratory cancer patients in 4 hospitals and from cancer registry.	1,773 cancer-free persons recruited by Parish Sisters of 2 institutes in all parts of the country.	Cases: From case histories or mailed questionnaires. Controls: Questionnaires distributed by Parish Sisters.
Haenszel et al., 1962, U.S.A. (*112*).	M	2,191 sample of 10 percent of white male lung cancer deaths in the U.S.A. in 1958.	31,516 random sample from Current Population Survey.	Cases: By mail from certifying physicians and family informants. Controls: Personal interview by census enumerators.
Lancaster, 1962, Australia (*158*).	M	238 hospital patients with lung cancer.	476 in 2 groups, 1 with other cancer, 1 with some other disease, matched by sex and age.	Personal interviews of both cases and controls in hospitals.
Haenszel and Taeuber, 1964, U.S.A. (*115*).	F	740 sample of 10 percent of white female lung cancer deaths in the U.S.A. in 1958 and 1959.	34,339 random sample from Current Population Survey used to estimate population base.	Cases: By mail from certifying physicians and family informants. Controls: Personal interview by census enumerators.

TABLE A3.—*Outline of methods used in retrospective studies of smoking in relation to lung cancer (cont.)*

Author, year, country, reference	Sex of cases	Number of persons and method of selection		Collection of data
		Cases	Controls	
Wicken, 1966, Northern Ireland (303).	M-F	954 patients with primary lung cancer.	954 age and sex-matched controls from same locale and deceased from nonrespiratory diseases.	Interviews with relatives.
Gelfand et al., 1968, Rhodesia (99).	M	92 patients with bronchogenic cancer.	92 age and sex-matched patients	Hospitalization interviews.
Hitosugi, 1968, Japan (126).	M-F	185 patients with lung cancer	491 persons sex-matched from similar air-pollution regions.	Cases: Hospital interviews. Controls: Interviews by trained public health nurses.
Bradshaw and Schonland, 1969, South Africa (Natal) (47).	M	45 Zulu patients with lung cancer.	341 Zulu patients without lung cancer.	Interviewed by trained African social worker.
Ormos et al., 1969, Hungary (204).	M-F	118 patients with lung cancer.	3,089 control persons without data on health history.	Cases: Data derived from case histories and interviews with relatives. Controls: Interviews with a random sample of train passengers.
Wynder, et al., 1970 U.S.A. (324).	M-F	240 patients with Kreyberg Type I lung cancer.	480 age and sex-matched patients	Hospitalization interview.

TABLE A4.—*Group characteristics in retrospective studies on lung cancer and tobacco use*

SM = Smokers. NS = Nonsmokers.

Author, year, reference	Males							Females							Comments
	Cases			Controls			Relative risk ratio SM:NS[2]	Cases			Controls			Relative risk ratio SM:NS[2]	
	Number	Percent non-smokers	Percent heavy smokers[1]	Number	Percent non-smokers	Percent heavy smokers[1]		Number	Percent non-smokers	Percent heavy smokers[1]	Number	Percent non-smokers	Percent heavy smokers[1]		
Müller, 1939 (*196*).	86	3.5	65.1	86	16.3	36.0	[3]5.4	(4)	(4)	(4)	(4)	(4)	(4)	...	
Schairer and Schöniger, 1943 (*242*).	93	3.2	31.2	270	15.9	9.3	[3]5.7	(4)	(4)	(4)	(4)	(4)	(4)	...	16 female cases not analyzed.
Potter and Tully, 1945 (*212*).	43	7.0	30.2	2,804	26.0	23.0	[3]4.1	(4)	(4)	(4)	(4)	(4)	(4)	...	
Wassink, 1948 (*304*).	134	4.8	54.8	100	19.2	19.2	4.7	(4)	(4)	(4)	(4)	(4)	(4)	...	Percentages estimated from chart.
Schrek et al., 1950 (*246*).	82	14.6	18.3	522	23.9	9.2	1.8	(4)	(4)	(4)	(4)	(4)	(4)	...	
Mills and Porter, 1950 (*186*).	444	7.2	...	430	30.5	...	5.7	(4)	(4)	(4)	(4)	(4)	(4)	...	
Levin et al., 1950 (*171*).	236	15.3	...	481	21.7	...	1.5	(4)	(4)	(4)	(4)	(4)	(4)	...	Quantity smoked not considered.
Wynder and Graham, 1950 (*316*).	605	1.3	51.2	780	14.6	19.1	13.0	40	57.5	25.0	552	79.6	1.2	2.9	

TABLE A4.—*Group characteristics in retrospective studies on lung cancer and tobacco use (cont.)*

SM = Smokers. NS = Nonsmokers.

Author, year, reference	Males							Females							
	Cases			Controls			Relative risk ratio SM:NS[2]	Cases			Controls			Relative risk ratio SM:NS[2]	Comments
	Number	Percent non-smokers	Percent heavy smokers[1]	Number	Percent non-smokers	Percent heavy smokers[1]		Number	Percent non-smokers	Percent heavy smokers[1]	Number	Percent non-smokers	Percent heavy smokers[1]		
McConnell et al., 1952 (*180*).	93	5.4	38.6	186	6.5	23.2	1.2	7	57.1	...	14	78.6	...	2.8	
Doll and Hill, 1952 (*79*).	1,357	0.5	25.1	1,357	4.5	13.4	9.4	108	37.0	11.1	108	54.6	0.9	2.1	Percentage "heavy" smokers understated.
Sadowsky et al., 1953 (*232*).	477	3.8	...	615	13.2	...	3.9	(4)	(4)	(4)	(4)	(4)	(4)	...	Gradient with amount smoked.
Wynder and Cornfield, 1953 (*314*).	63	4.1	67.6	133	20.6	20.3	[3]6.1	(4)	(4)	(4)	(4)	(4)	(4)	...	
Koulumies 1953 (*151*).	812	0.6	58.9	300	18.0	25.0	36.0	...	...	...	(4)	(4)	(4)	...	
Lickint 1953 (*170*).	224	1.8	35.8	1,000	16.0	4.8	[3]10.4	22	64.0	4.5	1,002	90.4	0.1	5.3	
Breslow et al., 1954 (*42*).	493	3.7	74.1	518	10.8	42.7	3.2	...	...	...	...	...	...	....	
Watson and Conte, 1954 (*305*).	205	1.9	71.7	287	9.7	51.6	[3]5.6	36	58.3	2.8	181	82.0	1.1	3.3	
Gsell, 1954 (*107*).	135	0.7	68.1	135	16.0	14.0	[3]26.8	(4)	(4)	(4)	(4)	(4)	(4)	...	

TABLE A4.—*Group characteristics in retrospective studies on lung cancer and tobacco use (cont.)*

SM = Smokers. NS = Nonsmokers.

Author, year, reference	Males							Females							Comments
	Cases			Controls			Relative risk ratio SM:NS[2]	Cases			Controls			Relative risk ratio SM:NS[2]	
	Number	Percent nonsmokers	Percent heavy smokers[1]	Number	Percent nonsmokers	Percent heavy smokers[1]		Number	Percent nonsmokers	Percent heavy smokers[1]	Number	Percent nonsmokers	Percent heavy smokers[1]		
Randig, 1954 (*218*).	415	1.2	34.2	381	5.8	17.9	[3]5.1	33	51.6	3.0	131	70.3	0	2.2	
Wynder et al., 1956 (*311*).	(4)	(4)	(4)	(4)	(4)	(4)	...	105	56.2	16.2	1,304	66.0	3.4	1.4	
Segi et al., 1957 (*250*).	166	...	...	2,124	...	...	...	...	...	...	...	...	...	...	Quantities smoked stated as averages only. Differences are statistically significant.
Mills and Porter, 1957 (*187*).	484	8.4	26.0	1,588	27.6	5.3	4.2	94	83.0	4.3	1,722	73.3	0.5	0.6	Percent "heavy" smokers understated. Only 50% survey response among female cases.
Stocks, 1957 (*263*).	2,101	1.9	28.2	5,960	8.7	22.3	4.9	255	57.6	17.2	3,402	68.6	10.7	1.6	
Schwartz and Denoix, 1957 (*247*).	602	1.0	58.2	1,204	9.5	36.2	10.4	(4)	(4)	(4)	(4)	(4)	(4)	...	
Haenszel and Shimkin, 1958 (*113*).	(4)	(4)	(4)	(4)	(4)	(4)	...	158	51.9	14.6	339	69.6	8.2	2.5	

TABLE A4.—*Group characteristics in retrospective studies on lung cancer and tobacco use (cont.)*

SM = Smokers. NS = Nonsmokers.

Author, year, reference	Males							Females							Comments
	Cases			Controls			Relative risk ratio SM:NS[2]	Cases			Controls			Relative risk ratio SM:NS[2]	
	Number	Percent nonsmokers	Percent heavy smokers[1]	Number	Percent nonsmokers	Percent heavy smokers[1]		Number	Percent nonsmokers	Percent heavy smokers[1]	Number	Percent nonsmokers	Percent heavy smokers[1]		
Lombard and Snegireff, 1959 (*176*).	500	1.6	...	4,238	11.0	...	7.9	(4)	(4)	(4)	(4)	(4)	(4)	...	Authors' calculations for heavy smoking based on lifetime number of packs of cigarettes.
Pernu, 1960 (*211*).	1,477	6.6	34.5	713	37.2	20.8	8.4	129	85.3	20.4	1,060	91.6	0.7	1.9	Quantities given only in grams per day.
Haenszel et al., 1962 (*112*).	2,191	3.4	41.9	(4)	16.2	12.0	5.2	(4)	(4)	(4)	(4)	(4)	(4)	...	Population sample of 31,516 used as base. Not a case-control study.
Lancaster, 1962 (*158*).	238	2.5	86.1	476	20.1	71.2	9.8	(4)	(4)	(4)	(4)	(4)	(4)	...	
Haenszel and Taeuber, 1964 (*115*).	(4)	(4)	(4)	(4)	(4)	(4)	...	749	60.9	11.5	(4)	67.3	2.5	1.3	Population sample of 34,339 used as base. Not a case-control study.

TABLE A4.—*Group characteristics in retrospective studies on lung cancer and tobacco use (cont.)*

SM = Smokers. NS = Nonsmokers.

Author, year, reference	Males							Females							Comments
	Cases			Controls			Relative risk ratio SM:NS[2]	Cases			Controls			Relative risk ratio SM:NS[2]	
	Number	Percent nonsmokers	Percent heavy smokers[1]	Number	Percent nonsmokers	Percent heavy smokers[1]		Number	Percent nonsmokers	Percent heavy smokers[1]	Number	Percent nonsmokers	Percent heavy smokers[1]		
Wicken, 1966 (*308*).	803	4.0	40.0	803	14.0	22.0	3.9	151	58.0	29.0	151	80.0	17.0	2.0	Heavy smokers—greater than 23 a day.
Gelfand et al., 1968 (*98*).	32	6.3	...	32	63.0	...	[3]25.3	(4)	(4)	(4)	(4)	(4)	(4)	...	
Hitosugi, 1968 (*125*).	124	5.6	67.8	1,839	13.2	55.0	2.6	61	54.1	6.6	2,352	80.5	2.9	2.3	Air pollution found to have no effect on lung cancer rates of nonsmokers. Heavy smokers—greater than 15 a day.
Bradshaw and Schonland, 1969 (*41*).	45	0.0	...	341	31.7	...	...	(4)	(4)	(4)	(4)	(4)	(4)	...	
Ormos et al., 1969 (*204*).	94	7.5	68.5	1,611	42.9	38.9	9.3	24	95.8	0.0	1,278	81.7	9.7	0.2	Heavy smokers—greater than 15 a day.
Wynder et al., 1970 (*334*).	210	1.4	67.5	420	21.0	40.9	[3]20.8	30	16.7	44.0	132	57.6	23.3	6.78	Heavy smokers—greater than 20 a day.

[1] For this table, heavy smokers are defined as those smoking 20 or more cigarettes per day, unless otherwise stated.

[2] Computed according to method of Cornfield, J. (61).

[3] Based upon fewer than 5 case nonsmokers.

[4] Does not apply.

TABLE A7.—*Grouping of pulmonary carcinomas*

Group I:
- A. Epidermoid carcinoma.
- B. Small cell anaplastic carcinoma ("oat-cell" carcinoma).

Group II:
- A. Adenocarcinoma.
- B. Bronchiolo-alveolar cell carcinoma.
- C. Carcinoid tumor.
- D. Mucous gland tumor.

Extra (not included in I and II):
- A. Large cell undifferentiated carcinoma.
- B. Combined epidermoid and adenocarcinoma.

Unsuitable for diagnosis.

SOURCE: Kreyberg, L. (*153*).

TABLE A12.—*Autopsy studies concerning the presence of radioactivity in the lungs of smokers*

NS = Nonsmokers. SM = Smokers.

Author, year, country, reference	Number of cases	Results					Comments
Little et al., 1964, U.S.A. (*173*).		*Po^{210} levels in various tissues (pc/g tissue)*					Vertebral bodies, renal cortex, spleen, and urinary bladder showed no differences.
		Peribronchial lymph nodes		*Lung (average)*		*Bronchial epithelium*	
	NS 5	0.011		0.001-2		negligible	
	SM 12	0.011		0.008		0.028-1.25	
Hill, 1965, U.S.A. (*125*).		*Mean Po^{210} levels in various tissues (pc/kg tissue)*					The authors found no excessive concentrations at bronchial bifurcations.
		Bronchial tree	*Alveolae*	*Total lung*	*Liver*	*Kidney*	
	NS 6	3.1	3.4	3.2	14.8	15.0	
	SM 4	7.3	9.9	8.6	20.0	20.5	
Little et al., 1965, U.S.A. (*174*).		*Po^{210} levels in various epithelial tissue regions of lung (pc/g)*†					The authors noted considerable interpersonal variation but did find a trend relationship between increased daily consumption and increased Po^{210} levels in lung parenchyma. No such relationship was noted for age of individual at death or for total pack-years.
		Site:					
	NS..... 8	Mainstem bronchus				<0.2- 1.7	
	SM 25	Lobar bronchus				<0.2- 1.0	
		Basal segmental bronchus				<0.2- 2.6	
		Upper segmental bifurcation				<0.5- 7.8	
		Lower segmental bifurcation				<0.5-13.9	

† Smokers only.

TABLE A12.—*Autopsy studies concerning the presence of radioactivity in the lungs of smokers (cont.)*

NS = Nonsmokers. SM = Smokers.

Author, year, country, reference	Number of cases	Results			Comments
Ferri and Baratta, 1966, U.S.A. (*95*).		*Mean Po^{210} levels in various tissues (pc/g wet tissue)*			
		Lung	*Liver*	*Kidney*	
	NS 10	0.031	0.103	0.080	
	SM 14	0.065	0.125	0.070	
Rajewsky and Stahlhofen, 1966, Germany (*217*).		*Mean Po^{210} levels in various tissues (pc/g)*			† Data not given. Smokers were considered those using more than 1 pack a day. The authors noted that their figures were considerably smaller than those of Little et al. (*173, 174*) and also disagreed with their data on bifurcation.
		Lung parenchyma	*Bronchial tree*	*Bronchial bifurcation*	
	NS ..... †	0.0025	0.0020	0.0012	
	SM 12	0.0078	0.0077	0.0047	
Little and Radford, 1967, U.S.A. (*173*).		*Mean Po^{210} levels in various epithelial tissues (pc/g wet tissue)*			
	SM 25	Bronchial wall and submucosa 0.004			
		Bronchial epithelium:			
	Pipe 2	Trachea 0.120			
	Ex-cigarette 1	Lobar bronchi 0.190			
	Never 8	Segmental bifurcation 4.500			

TABLE A13.—*Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals*

Author, year, country, reference	Animal and strain	A. Method, B. Frequency and/or duration, C. Material	Results			Comments
Wynder et al., 1953, U.S.A. (*317*).	CAF_1 mice	A. Painting shaved skin. B. 3/week for 2 years. C. Whole cigarette smoke condensate in acetone. Croton oil once/week.	*Percent animals with:* *Treatment:*	*Papillomas*†	*Cancer*†	† Number in parenthesis represents total in that experimental group. Skin-painting experiments prior to 1953 are fully detailed in tabular form in this article.
			"Tar" alone	59.0(81)	44.0(81)	
			"Tar" and croton oil	42.0(31)	9.7(31)	
			Acetone alone	(30)	(30)	
			Acetone and croton oil	(14)	(14)	
Passey et al., 1955, England (*209*).	5 different mouse strains (*101*).	A. Painting unshaven skin. B. 2/week for 9 months. C. Whole "tar" or neutral fraction.	No malignant tumors noted in either group. Papilloma noted on one animal (in whole "tar" group) which later regressed.			
Orr et al., 1955, England (*205*).	Mice of 2 strains.	A. Painting skin. B. 1 or 2/week for 18 months. C. 20 percent cigarette "tar" in acetone. 0.3 percent benzpyrene.	*Number animals with:* *Treatment:*	*Papillomas*		
			Benzpyrene 1/week followed by "tar" 2/week.	4/30 at 18 months (separate group received only benzpyrene and showed no tumors).		
			"Tar" alone	0/50 at 18 months.		

TABLE A13.—*Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals (cont.)*

Author, year, country, reference	Animal and strain	A. Method, B. Frequency and/or duration, C. Material	Results	Comments
Wynder et al., 1955, U.S.A. (*318*).	Mice of 4 separate strains.	A. Painting shaved skin. B. 3/week for 80 days. C. Whole condensate in acetone.	*Strain* — *Papillomas* — *Carcinomas* C57BL ..... 10/89 — 2/89 Swiss ..... 22/86 — 12/86	No tumors noted with acetone alone. Stresses differences in susceptibility of strain.
Hamer and Woodhouse, 1956, U.S.A. (*116*).	Outbred albino strain mice.	A. Painting unshaved skin. B. Varied for 18 months. C. Whole "tar"/acetone, benzpyrene [B(a)P], croton oil.	*Treatment:* — *Papillomas* "Tar" 2/week ..... 1/60 "Tar" and croton oil 1/week. ..... 2/30 B(a)P 3 times then "tar" 2/week ..... 4/30 B(a)P 3 times 0/30	
Sugiura, 1956, U.S.A. (*266*).	Rockland Swiss albino mice (60).	A. Painting unshaved skin. B. 3/week for 2 years. C. Whole "tar".	*Papillomas* 16/44 — *Carcinomas* 12/44 (only 44/60 lived from 365–696 days).	
Graham et al., 1957, U.S.A. (*101*).	Albino New Zealand rabbits.	A. Painting shaved skin. B. 3/week for 6 years. C. Whole condensate.	*Treatment:* — *Papillomas* — *Carcinomas* Condensate ..... 41/41 — 5/41 Condensate and croton oil 1/week. 10/10 — 2/10 Croton oil and acetone 1/week. 0/3 — 0/3 Acetone 1/week ..... 0/7 — 0/7	The authors review previous experiments with rabbits in tabular form.
Guerin and Cuzin, 1957, U.S.A. (*109*).	Mice (Pasteur strain.)	A. Painting neck skin. B. 2/week for >1 year. C. Whole condensate.	*Original number* — *Survivors* — *Papillomas* — *Sarcomas* †C. 112 ..... 51 — 0/51 — 0/51 ‡E. 672 ..... 220 — 10/220 — 5/220	† Control group. ‡ Experimental group.

TABLE A13.—*Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals (cont.)*

Author, year, country, reference	Animal and strain	A. Method, B. Frequency and/or duration, C. Material	Results				Comments
Wynder et al., 1957, U.S.A. (*329*).	Swiss mice	A. Painting skin. B. Varied for 12 months. C. Whole condensate in acetone.	*Treatment:*	*Number*	*Percent papillomas*	*Percent carcinomas*	
			5/week	50	12.0	8.0	
			3/week	50	38.0	16.0	
			2/week	40	10.0	3.0	
			1/week	40	6.0	...	
Wynder and Wright, 1957, U.S.A. (*328*).	CAF_1 or Swiss mice.	A. Painting shaved skin. B. 3/week for lifespan. C. Whole "tar" or nicotine free "tar" derived from pipe and cigarette tobacco.	*Treatment CAF_1:*	*Number*	*Percent papillomas*	*Percent carcinomas*	Swiss mice noted to be more susceptible. Majority of carcinogens noted to be in neutral fraction of condensate.
			Whole "tar"	30	53.0	27.0	
			Nicotine free "tar"	40	73.0	25.0	
			Cigarette "tar"	30	30.0	30.0	
			Pipe "tar"	30	60.0	20.0	
			Treatment Swiss:				
			Whole "tar"	30	53.0	10.0	
			Nicotine free "tar"	40	43.0	20.0	
			Cigarette "tar"	30	63.0	33.0	
			Pipe "tar"	30	63.0	50.0	
Gellhorn, 1958, U.S.A. (*99*).	Paris R III mice	A. Painting shaved skin. B. Varied for 1–2 years. C. "Tar" in acetone, benzpyrene, croton oil.	*Treatment:*		*Papillomas*	*Carcinomas*	
			Benzpyrene (twice only)		20/529	5/529	
			Croton oil (5/6 week)		4/26	0/26	
			"Tar" (5/6 week)		3/559	2/559	
			Acetone (5/6 week)		0/30	0/30	
			"Tar" and croton oil (5/6 week)		10/175	0/175	
Bock and Moore, 1959, U.S.A. (*23*).	Swiss female mice	A. Painting skin. B. 5/week for lifespan. C. Whole condensate irradiation.	Group:	*Number living at 6 months*		*Percent Skin tumors at 64 weeks*	
			Painted	49		13.0	
			Painted and irradiated	65		44.0	
			Irradiated	30		...	

TABLE A13.—*Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals (cont.)*

Author, year, country, reference	Animal and strain	A. Method, B. Frequency and/or duration, C. Material	Results			Comments
Druckrey, 1961, Germany (*78*).	Rats	A. Subcutaneous injection. B. 1/week for 60 weeks. C. Smoke condensate in tricaprylin and alcohol.	*Group:* † C ‡ E		*Sarcomas* 1/75 15/75	† Control group. ‡ Experimental group.
Bock et al., 1962, U.S.A. (*31*).	ICR Swiss mice	A. Painting shaved skin. B. 10/week for 1 year. C. Cigarette "tar".	*Treatment:*	*Surviving at 18 weeks*	*Percent Skin cancer*	*Percent Skin neoplasia*
			Standard cigarette	24/30	25.0	54.0
			Standard cigarette	21/30	5.0	57.0
			Standard cigarette	18/30	33.0	44.0
			Standard cigarette	13/30	23.0	62.0
			Filter cigarette	30/30	7.0	27.0
			Filter cigarette	30/30	3.0	23.0
			Acetone only	66/66	...	...
			Control	65/65	...	...
Roe, 1962, U.S.A. (*225*).	Albino mice	A. Painting shaved skin. B. 3/week for 84 weeks. C. Whole smoke "tar" with added B(a)P in acetone.	Treatment:	*Survivors*	*Percent skin tumors*	Author concluded that cigarette smoke contains cocarcinogens.
			"Tar" and 0.025 mg. B(a)P	26	12.0	
			"Tar" and 0.06 mg. B(a)P	15	27.0	
			"Tar" and 0.25 mg. B(a)P	15	13.0	
			"Tar" and 1.25 mg. B(a)P	14	64.0	
			B(a)P 1.25 mg.	14	...	
Druckrey and Schildbach, 1963, Germany (*82*).	Rats	A. Subcutaneous injection. B. 1/week for 700 days. C. Benzpyrene in tricaprylin.	*Treatment (BP mg./week):*		*Sarcomas*	
			30		25/30	
			10		14/40	
			3		8/60	
			— (solvent)		2/75	

TABLE A13.—*Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals (cont.)*

Author, year, country, reference	Animal and strain	A. Method, B. Frequency and/or duration, C. Material	Results				Comments
Homburger et al., 1963, U.S.A. (*151*).	CAF_1 mice	A. Painting shaved skin. B. 2–3/week for 2 years. C. Various tobacco condensates in acetone.	*Condensate:*	*Complete autopsies*	*Percent Papillomas*	*Percent Carcinomas*	
			Pipe tobacco	77	35.0	15.0	
			Cigar tobacco	84	27.5	16.0	
			Cigarette tobacco	82	27.0	16.0	
			Benzpyrene	54	10.0	20.0	
			Acetone only	62	...	...	
Bock et al., 1965, U.S.A. (*29*).	Swiss ICR mice	A. Painting clipped skin. B. 10/week for 11 weeks. C. Various smoke condensates in acetone.	Percent concentration of tar (type cigarette):	*Percent surviving 11 weeks*	*Percent cancer*	*Percent cancer and papilloma*	
			9.2 (standard)	96.0	30.0	67.0	
			8.3 (standard)	93.0	27.0	67.0	
			7.9 (English standard)	90.0	24.0	55.0	
			8.7 (king)	100.0	28.0	69.0	
			4.0 (filter)	98.0	9.0	36.0	
			4.4 (filter)	100.0	10.0	41.0	
			2.5 (filter)	97.0	4.0	16.0	
			Acetone control	94.0	...	...	
			Untreated control	100.0	...	...	
Van Duuren et al., 1966, U.S.A. (*296*).	Swiss ICR/Ha mice	A. Painting shaved skin. B. Initiating agent once—Promoter 3/week for 12–14 months. C. DMBA†, tobacco extracts cigarette "tar"	*Initiator* *Promoter*		*Cumulative number of mice with Papillomas*	*Carcinomas*	† 7,12-dimethylbenz(a)anthracene.
			DMBA ...Ether tobacco leaf extract		4/20	0/20	
			O .....Ether tobacco leaf extract		0/20	0/20	
			DMBA ...Chloroform tobacco leaf extract		1/20	0/20	
			O .....Chloroform tobacco leaf extract		0/20	0/20	
			DMBA ...Cigarette "tar"		11/20	4/20	
			O .....Cigarette "tar"		0/20	0/20	
			O .....Acetone		0/20	0/20	

TABLE A13.—*Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals (cont.)*

Author, year, country, reference	Animal and strain	A. Method B. Frequency and/or duration, C. Material	Results				Comments
Munoz et al., 1968, U.S.A. and Colombia (*197*).	Swiss ICR/4a mice	A. Painting shaved skin. B. Varied. C. "Tar" from dark (Colombian) and light (U.S.A.) tobaccos.	*Dark tobacco "tar"*	*At risk*	*Tumors*	*Carcinomas*	The authors noted a shortened latent period for dark tobacco.
			4.0 percent	81	50	17	
			8.0 percent	71	46	16	
			Light tobacco tar:				
			4.0 percent	95	26	6	
			8.0 percent	98	54	20	
			Acetone	91	0	0	
Davies and Day, 1969, Great Britain (*65*).	Albino mice	A. Painting shaved skin. B. Varied regimen. C. Cigarette and cigar condensate.	*Percent of carcinoma-bearing animals at 116 weeks (actual number of animals in parentheses)*				The authors concluded that the lack of difference in results from the first and third groups under treatment suggests that the increased tumorigenicity of cigar tobacco is due to physical processing factors.
			Treatment:	*300 mg.*	*150 mg.*	*75 mg.*	*37.5 mg.*
			Standard cigarette	20.1(29)	13.2(19)	0.7 (1)	..
			Cigar	..	27.1(39)	11.1(16)	2.1(3)
			Cigar tobacco cigarette	..	13.9(19)	..	..

TABLE A14.—*Experiments concerning the effect of cigarette smoke or its constituents on tissue and organ cultures*

Author, year, country, reference	Tissue or organ culture	Material/delivery	Results
Bouchard and May, 1960, France (*35*).	Mouse lung.	Tobacco smoke condensate perfusion for 24 hours and subsequent grafting under renal capsule of mice.	Increased number of mitotic abnormalities in the treated cultures; particularly in the first 5–10 days after grafting.
Awa et al., 1961, Japan (*16*).	Human fetal lung.	Direct exposure to smoke from: a. Whole cigarettes. b. Tobacco alone. c. Paper alone.	Paper smoke induced the most severe changes, consisting of cytoplasmic vacuolization and nuclear pyknosis. Also noted were a decrease in the mitotic index and an increase in abnormal divisions, more so with paper smoke than with the other two.
Thayer and Kensler, 1964, U.S.A. (*275*).	KB mammalian tumor cells.	Cigarette smoke condensate application; filtered and unfiltered cigarettes.	Significant growth inhibition was shown in unfiltered smoke. Cytotoxic components were noted in both the gas and particulate phases.
Berwald and Sachs, 1965, Israel (*20*).	SWR mice and golden hamster embryos.	Direct application of benzo(a)pyrene [B(a)P].	Benzo(a)pyrene caused increased cell transformation as manifested by: a. Hereditary random growth pattern. b. Progressive growth as tumors after subcutaneous injection into adults. c. Ability to grow continuously in culture.
Crocker et al., 1965, U.S.A. (*63*).	Suckling rat trachea in organ culture.	Application of B(a)P in acetone.	Treated cultures revealed cellular metaplasia, basal cell hyperplasia, increased mitotic rate, and increased H^3-thymidine incorporation proportional to the concentration of material and duration of application.
Diamond, 1965, U.S.A. (*68*).	Various continuous cell strains (mammalian).	Application of B(a)P in either dimethylsulfoxide (DMSO) or paraffin.	Inhibition of cell growth.

TABLE A14.—*Experiments concerning the effect of cigarette smoke or its constituents on tissue and organ cultures (cont.)*

Author, year, country, reference	Tissue or organ culture	Material/delivery	Results
Borenfreund et al., 1966, U.S.A. (*53*).	Hamster lung tissue.	Application of B(a)P in either DMSO or dimethyl-formamide.	a. Increased appearance of new small chromosomes and telocentric chromosomes. b. Increased ability to grow in hamster cheek pouch and there become spindle-cell sarcomas.
Guimard, 1966, France (*110*).	Chicken embryo muscular explants.	Application of tobacco extract.	Increased mitotic activity and increased incidence of anomalous mitoses.
Lasnitzki, 1968, England (*160*).	Mice neonatal trachea.	Application of a hydrocarbon-enriched fraction of whole smoke condensate.	a. Increased basal cell hyperplasia and pleomorphism of newly formed cells. b. Increased epithelial mitosis.
Lasnitzki, 1968, England (*161*).	Human fetal lung in organ culture.	Application of a hydrocarbon-enriched fraction of whole smoke condensate.	a. Cellular enlargement and promotion of growth of new bronchi. b. Increased mitoses, bronchial epithelial hyperplasia, and squamous metaplasia. c. Inhibition of stromal growth.
Chan et al., 1969, U.S.A. (*54*).	Mouse lung bud embryonic cultures.	Application of B(a)P in DMSO.	a. Cellular disorganization. b. Cellular pyknosis; nuclear shape and size irregularities. c. Increased epithelial mitotic rate and decreased mesenchymal mitotic rate in those cultures exposed to B(a)P versus those exposed to pyrene or DMSO.
Leuchtenberger and Leuchtenberger, 1969, Switzerland (*165*).	Mouse lung and kidney tissue and organ cultures.	Exposure to fresh smoke: a. Unfiltered. b. Activated charcoal filter. c. Cigarette or cigar tobacco.	a. Decreased RNA production, pyknosis, and death of cells. b. Similar results, but changes were of minimal severity. c. Similar effects as group a., but less severe.

TABLE A14.—*Experiments concerning the effect of cigarette smoke or its constituents on tissue and organ cultures (cont.)*

Author, year, country, reference	Tissue or organ culture	Material/delivery	Results
Crocker, 1970, U.S.A. (62).	Various organ cultures: a. Whole suckling hamster trachens. b. Whole bronchial tubes from late fetal dogs and monkeys.	Application of B(a)P in serum.	Squamous metaplusia; frequent pleomorphic cells; dedifferentiation of epithelium (inhibited by Vitamin A).

TABLE A15.—*Experiments concerning the effect of the instillation or implantation of cigarette smoke or its constituents into the tracheobronchial tree of animals*

Author, year, country, reference	Animal and strain	A. Method B. Frequency and/or duration C. Material	Results
Blacklock, 1957, Great Britain (24).	CB white rats.	A. Injection into lung parenchyma by thoracotomy. B. Once. C. 3,4-benzpyrene in olive oil, with dead Tb bacilli or in cholesterol, cigarette "tar".	3,4-benzpyrene: *Number with tumors/number exposed* a. 3 mg. in olive oil: 5/6 sarcoma. b. 3 mg. in olive oil with dead Tb bacilli: 2/4 sarcoma, 4/8 squamous cell carcinoma. c. 5.75 mg. in cholesterol pellet: 1/8 squamous cell carcinoma. Cigarette "tar": a. In olive oil: 0/10. b. In olive oil with dead Tb bacilli: 1/8 sarcoma, 1/8 squamous cell carcinoma. Controls: a. 0.15 cc. olive oil: 0/4. b. 0.15 cc. olive oil with dead Tb bacilli: 0/4. c. Cholesterol pellets: 0/4.

Author, year, country, reference	Animal and strain	A. Method B. Frequency and/or duration C. Material	Material:	*Weeks*	*Survivors at 20 weeks/original number exposed*	*Number of hamsters with tracheobronchial carcinomas at death*
Della Porta et al., 1958, U.S.A. (67).	Syrian golden hamsters.	A. Direct tracheal instillation. B. Weekly up to 45 weeks. C. 1 percent 7,12-dimethylbenz(a)anthracene (DMBA), cigarette "tar" concentrate.	a. DMBA 50 μg./week	45	10/20	2
			b. "Tar" 200 μg./week	32	11/21	—
			c. DMBA 50 μg./week ..... then "tar" 200 μg./ week	12 30	9/20 —	— —
			d. DMBA 100 μg./week	17	7/20	4
			e. DMBA 100 μg./week and "tar" 500 μg./week	20	9/20	3

Author, year, country, reference	Animal and strain	A. Method B. Frequency and/or duration C. Material	Results
Rigdon, 1960, U.S.A. (221).	White Pekin ducks. Controls: 99 Experimental group: 52	A. Intratracheal injection. B. Daily for 721 days. C. Tobacco condensate in liquid petrolatum.	No neoplastic changes noted in either the experimental or control groups.

TABLE A15.—*Experiments concerning the effect of the instillation or implantation of cigarette smoke or its constituents into the tracheobronchial tree of animals (cont.)*

Author, year, country, reference	Animal and strain	A. Method B. Frequency and/or duration C. Material	Results
Blacklock, 1961, Great Britain (*25*).	CB white rats.	A. Inoculation at thoracotomy. B. Once and sacrificed at 1 week-2 years. C. Cigarette tobacco smoke condensate in eucerin.	*Number of rats* / *Percent with malignant tumors* Controls ..... 275 — 1.5 (1 carcinoma, 3 sarcomas). Cigarette condensate ..... 72 — 11.1 (6 carcinomas, 2 sarcomas). Eucerin alone ..... 44 — 2.3 (1 sarcoma).
Herrold and Dunham, 1962, U.S.A. (*122*).	Syrian golden hamsters.	A. Intratracheal inoculation. B. 0.5 cc./week for 5/6 months. C. Benzo(a)pyrene in Tween60 or olive oil.	Material: / *Number of hamsters* / *Number with tumors* / *Number of tracheobronchial tumors* B(a) in Tween60 ... 6 — 3 — 5 (3 papillomas, 2 carcinomas). B(a)P in Tween60[1] 6 — 3 — 9 (4 papillomas, 5 carcinomas). Tween60 ..... 6 — 0 — — B(a)P in olive oil .. 6 — 0 — — Olive oil ..... 6 — 0 — —
Rockey et al., 1962, U.S.A. (*224*).	Dogs.	A. Bronchial inoculation or stimulation. B. 3-5 times/week for up to 5 years. C. Cigarette smoke condensate.	Procedure: / *Number of dogs* / *Invasive carcinoma* / *Carcinoma-in situ* / *Pre-cancerous changes* / *Squamous metaplasia with atypical changes* / *Inflammation* Controls ..... 27 — — — 6 24 Manipulation of bronchus ..... 25 — — — 7 25 Smoke condensate 130 — 1 — 3 — 25 — 98 — 128
Tipton and Crocker, 1964, U.S.A. (*277*).	Mongrel dogs. Control group and experimental group—19.	A. Bronchial inoculation. B. Daily for 8 days. C. Cigarette smoke condensate.	Rapid induction of squamous metaplasia in condensate-exposed animals. No tabular data is presented.

TABLE A15.—*Experiments concerning the effect of the instillation or implantation of cigarette smoke or its constituents into the tracheobronchial tree of animals (cont.)*

Author, year, country, reference	Animal and strain	A. Method B. Frequency and/or duration C. Material	Results				
Saffiotti et al., 1968, U.S.A. (*237*).	Syrian golden hamsters.	A. Intratracheal inoculation. B. Weekly for 15 weeks. C. B(a)P (3 mg.) attached to fine hematite dust.	Number autopsied:	*Number of tumor-bearing animals*	*Percent tumor-bearing of survivors at 15 weeks*	*Total number of tumors*	*Total number of respiratory tract cancers*
			Male 23	15	100.0	24	18
			Female 17	11	100.0	17	16
Kuschner, 1968, U.S.A. (*157*).	Hamsters.	A. Wire mesh pellet implantation into bronchus. B. Lifetime. C. B(a)P, methylcholanthrene (MCA).	Implant:	*Number of survivors/original number in group*	*Number of animals with lung cancer*		
			Wire mesh only	34/35	—		
			MCA	88/91	43		
			B(a)P	89/91	57		
Saffiotti et al., 1968, U.S.A. (*235*).	Syrian golden hamsters.	A. Intratracheal inoculation. B. Weekly for 15 weeks. C. B(a)P attached to a fine hematite dust.	Inoculate:	*Number autopsied*	*Number of hamsters with respiratory tract tumors*		
			Control	176	—		
			B(a)P in hematite	55	35		
			Hemntite only	41	—		
Borisyuk, 1969, Russia (*34*).	Wistar rats.	A. Intratracheal intubation. B. Monthly up to 10 months. C. Cigarette "tar".	Inoculate:	*Number final/initial*	*Duration of inoculation (months)*		
			Controls	11/20	12		
			Unfractionated "tar"	24/200	10		
			Denicotinized "tar"	9/45	8 (1/9 metaplasia)		
			Neutral "tar" fraction	14/100	8 (2/14 carcinomas, 1/14 papillary adenoma).		

[1] This group also received one injection of urethane intraperitoneally.

TABLE A16.—*Experiments concerning the effect of the inhalation of cigarette smoke or its constituents upon the respiratory tract of animals*

(Figures in parentheses represent total number survivors in specific group)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results	Comments
Lorenz et al., 1943, U.S.A. (177).	Strain A mice: †C. 97. ‡E. 97.	A. Chamber. B. Up to 693 hours. C. Cigarette smoke.	E. No increase in tumor formation over that noted in controls.	This strain of mice does have a hereditary tendency to tumor formation. †C. Control. ‡E. Experimental.
Essenberg, 1952, U.S.A. (92).	Strain A mice: C. 32. E. 36.	A. Chamber. B. 12 hours per day for 1 year. C. Cigarette smoke.	*Percent of lung tumors* C. 50.4 (19) E. 91.3 (23)	No epidermoid cancer noted; papillary adenocarcinoma was most common. Percentage difference is significant at $p \leq 0.01$ level.
Mühlbock, 1955, Netherlands (195).	Hybrid (020 × DBA) mice: C. 32. E. 29.	A. Chamber. B. 2 hours per day for up to 684 days. C. Cigarette smoke.	*Percent with alveolar carcinomas* C. 31.0 E. 79.0	No other type of lung tumors were found.
Leuchtenberger et al., 1958, U.S.A. (166).	CF_1 albino mice: C. and E. 275.	A. Chamber. B. To 8 cigarettes per day from 11–201 days. C. Cigarette smoke.	*28 of the experimental mice showed:* 15 basal cell hyperplasia. 14 atypical basal cell hyperplasia. 7 dysplasia. 2 squamous cell metaplasia.	
Guerin, 1959, France (108).	IC and Wistar strain rats. C. 40. E. 100.	A. Chamber. B. 45 minutes per day from 2–6 months. C. Cigarette smoke.	*Percentage of rats with pulmonary tumors* C. 2.4 percent of 39 survivors. E. 5.1 percent of 68 survivors.	

TABLE A16.—*Experiments concerning the effect of the inhalation of cigarette smoke or its constituents upon the respiratory tract of animals (cont.)*

(Figures in parentheses represent total number survivors in specific group)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results	Comments
Leuchtenberger et al., 1960, U.S.A. (*167*).	Female CF_1 mice: C. 243. E. 360.	A. Chamber. B. ½–6 cigarettes per day for 1 month to 2 years. C. Cigarette smoke.	*Number of mice* / *Number of cigarettes* / *Exposure length (months)* / *Number with severe bronchitis; peribronchitis; atypical epithelial proliferation* 151 ..... 25–1,526 1–23 30 150 ..... 0 0 2 36 ..... 100– 200 1– 3 7 36 ..... 250– 500 4– 8 7 34 ..... 600–1,600 9–23 8 51 ..... 100– 400 3– 6 4 63 ..... 100– 400 3– 6 17	
Leuchtenberger et al., 1960, U.S.A. (*168*)	Female CF_1 mice: C. 166. E. 231.	A. Chamber. B. ½–8 cigarettes per day for 17–600 days. C. Cigarette smoke.	*Number of mice examined* / *Exposure (days)* / *Percent of mice with pulmonary adenomatous tumors* 81 ..... 0 56 39 ..... 17– 99 41 35 ..... 100–199 37 51 ..... 200–600 66	Presence of tumors showed an age-relationship independent of smoking exposure.
Ito, 1963, Germany (*206*).	Albino mice. C. 60. E. 189.	A. Chamber. B. Approximately 12 cigarettes per day for varying intervals. C. Cigarette smoke.	*Number of mice examined* C. 60 E. 189 *Exposure* None. Varying up to 24 months. *Number with lung tumors* 3 pulmonary adenomas. 21 pulmonary adenomas. 2 epithelial carcinomas.	

TABLE A16.—*Experiments concerning the effect of the inhalation of cigarette smoke or its constituents upon the respiratory tract of animals (cont.)*

(Figures in parentheses represent total number survivors in specific group)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results	Comments
Dontenwill and Wiebecke, 1966, Germany (77).	Golden hamsters. C. — E. 320	A. Chamber. B. Up to 4 cigarettes per day for up to 2 years. C. Cigarette smoke.	*Number of animals dead at 540 days* / *Daily average exposure (cigarettes)* / *Histologic findings in dead animals* 40 ..... 1 — 8/ 40 MET des 40 ..... 2 — 8/ 40 MET des 80 ..... 1–2 — 44/ 80 MET des (3 MET bronch, 2 PAP trach) 143 ..... 1–4 — 67/143 MET des (13 MET bronch, 8 PAP trach)	MET des = desquamative metaplasia. MET bronch = bronchial papillary metaplasia. PAP trach = tracheal papillomata or intense tracheal metaplasia.
Leuchtenberger and Leuchtenberger 1966, Switzerland (164).	CF_1 mice.	A. Chamber. B. Up to 1,000 hours. C. Cigarette smoke, exposure to influenza virus (PR8).		†Epithelial tissues of these animals showed an increased frequency of cellular atypism. The authors concluded that PR8 influenza virus may act as a cofactor in malignant transformation.

	Marked squamous cell metaplasia (percent)	*Marked dysplasia (percent)*	*Marked transgression of lung parenchyma (percent)*
Controls (*100*):			
Male	—	—	—
Female	—	—	—
Smoke exposed (*59*):			
Male	—	6.0	3.0
Female	—	—	—
Virus exposed (*59*):			
Male	11.0	21.0	13.0
Female	—	—	5.0
Smoke and virus exposed (*68*):			
Male	9.0	43.0	†18.0
Female	29.0	54.0	†33.0

TABLE A16.—*Experiments concerning the effect of the inhalation of cigarette smoke or its constituents upon the respiratory tract of animals (cont.)*

(Figures in parentheses represent total number survivors in specific group)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results	Comments
Rockey and Speer, 1966, U.S.A. (*223*).	Mongrel dogs: C. 11. E. 19.	A. Tracheal fenestration (*10*). Nostril inhalation (*9*). B. Tracheal fenestration—284 treatment days. Nostril inhalation—180 treatment days. C. Cigarette smoke.	Inflammation; Hyperplasia with atypical features; Squamous metaplasia with atypical features; Precancerous changes; Carcinoma in situ Controls (*11*) . 9 1 1 0 0 Tracheal fenestration (*10*) ... 10 5 6 1 †1 Nostril inhalation (*9*) . 6 0 0 0 0	†Carcinoma *in situ* noted in 5 separate sites in this animal.
Auerbach et al., 1967, U.S.A. (*10*).	Beagle dogs: C. 10 (2 with tracheostoma). E. 10.	A. Tracheostoma. B. Up to 12 cigarettes per day for up to 421 days. C. Cigarette smoke.	Controls, experimental: No histologic change in bronchial epithelium: *a.* 1 animal died at 24 days and no histologic change noted. *b.* 5 animals sacrificed at 421 days and nuclear atypism noted in all. *c.* 2 animals died at 229 and 278 days and nuclear atypism was noted but of lesser severity than in those sacrificed at 421 days.	
Harris and Negroni, 1967, England (*121*).	C57BL mice: C. 200. E. 1,437.	A. Chamber. B. Smoke—12 cigarettes per 20 mice for 12 minutes every other day for lifetime. C. Cigarette smoke, influenza virus aerosol, benzpyrene aerosol.	*Treatment* — *Number* — *Number of lung carcinomas* Controls ..... 200 0 Influenza aerosol alone ..... 682 15 Benzpyrene aerosol (4 exposures) ..... 200 2 Smoking ..... 200 8 (all adenocarcinomas) Influenza and benzpyrene ... 200 3 Influenza and smoking 155 3	This strain of mice is noted for its lack of spontaneous lung tumor formation. Animals exposed to cigarette smoke showed no hyperplastic epithelial changes such as those noted by Leuchtenberger.

TABLE A16.—*Experiments concerning the effect of the inhalation of cigarette smoke or its constituents upon the respiratory tract of animals (cont.)*

(Figures in parentheses represent total number survivors in specific group)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results	Comments
Wynder et al., 1968, U.S.A. (*327*).	Male C57BL6 mice: C. and E.—more than 40.	A. Chamber. B. Up to 315 cigarettes. C. Cigarette smoke, nitrogen dioxide, volatile acids and aldehydes found in cigarette smoke, swine influenza virus.	Conclusions:† No squamous cell respiratory cancer noted. This is attributed to the limitation of inhalation time (CO and nicotine acute effects) and to the anatomically and physiologically intricate nasal passage defense system. Exposure to cigarette smoke, NO_2, or volatile acids and aldehydes leads to reactive hyperplasia and metaplasia, both of which were noted to be reversible. Swine influenza virus exposure produced hyperplastic and metaplastic effects which could not be enhanced by subsequent exposure to cigarette smoke.	†Results not provided in tabular form.
Laskin et al., 1970, U.S.A. (*159*).	Rats: C. 45. E. 3.	A. Chamber. B. 1 hour per day for up to 690 days. C. Benzo(a)pyrene aerosol, SO_2 atmosphere (3.5 p.p.m.).	*Exposure* — *Number* — *Squamous cell carcinomas* Atmosphere controls ..... 3 0/3 Atmosphere plus benzo(a)-pyrene exposure ..... 21 2/21 SO_2 controls ..... 3 0/3 SO_2 plus benzo(a)-pyrene exposure 21 5/21	
Hammond et al., 1970, U.S.A. (*119*).	Beagle dogs.	See text	See text.	

TABLE A21.—*Outline of retrospective studies of tobacco use and cancer of the larynx*

Author, year, country, reference	Cases			Controls		Collection of data
	Sex	Number	Method of selection	Number	Method of selection	
Schrek et al., 1950, U.S.A. (246).	M.	73	Referrals from V.A. hospitals in "entire midwest" to V.A. Cancer Center, Hines, Illinois, during 1942-44; patients with larynx-pharynx tumors clinically or histologically diagnosed: *Percent* Nonsmokers ..... 13.7 Cigarettes ..... 79.5 Cigars ..... 3.7 Pipes 6.8	522	From same set of referrals, patients with tumors other than lip, lung, larynx-pharynx: *Percent* Nonsmokers ..... 23.9 Cigarettes ..... 59.2 Cigars ..... 10.0 Pipes 11.5	Random sample of 6,003 admissions; questionnaires from Hines referrals for 1942-44; records included smoking history.
Valko, 1952, Czechoslovakia (292).	M-F	226	Clinic patients with cancer of the larynx: *Percent* Nonsmokers ..... 7.5 Cigarettes ..... 83.2 Cigars ..... 4.4 Pipes 10.6	108	Clinic patients of same age group with other diagnoses: *Percent* Nonsmokers 22.2	Medical history and questionnaire in clinic.
Sadowsky et al., 1953, U.S.A. (232).	M.	273	White male admissions to hospitals in New York City, Missouri, New Orleans, Chicago; patients with diagnosed laryngeal tumors, 1938-43: *Percent* Nonsmokers ..... 4.0 Cigarettes only ..... 60.1 Cigars only ..... 2.2 Pipe only ..... 4.8 Some combination 28.9	615	From same set of admissions, patients with illnesses other than cancer: *Percent* Nonsmokers ..... 13.2 Cigarettes only ..... 53.3 Cigars only ..... 3.4 Pipe only ..... 7.0 Some combination 23.1	Sample of 2,605 out of 2,847 interviews (including smoking history) by trained lay interviewers.

TABLE A21.—*Outline of retrospective studies of tobacco use and cancer of the larynx (cont.)*

Author, year, country, reference	Cases			Controls		Collection of data
	Sex	Number	Method of selection	Number	Method of selection	
Blümlein, 1955, Germany (*26*).	M.	241	Clinic patients with cancer of larynx: *Percent* Nonsmokers ..... 0.8 Heavy smokers ..... 79.3 Inhalers 95.0	200	Patients with no laryngeal disease: *Percent* Nonsmokers ..... 18.0 Heavy smokers ..... 4.3 Inhalers 17.0	Personal history taken in clinic. Patients and controls over 40 years of age.
Wynder et al., 1956, U.S.A. (*312*).	M.	209	White male inpatients Memorial Cancer Research Center during 1952 to 1954, with benign or malignant epidermoid tumors of larynx: *Percent* Nonsmokers ..... 0.5 Cigarettes ..... 86.0 Cigars ..... 7.5 Pipes ..... 5.0 Cigars/pipes 1.0	209	Patients with other than epidermoid cancer, individually matched controls in same institutions: *Percent* Nonsmokers ..... 10.5 Cigarettes ..... 73.7 Cigars ..... 10.1 Pipes ..... 3.8 Cigars/pipes 1.9	Trained lay interviewers.
Wynder et al., 1956, India (*312*).	M.	132	Laryngeal cancer patients at Tata Memorial Hospital, 1952–54: *Percent* Nonsmokers ..... 13.6 Bidis ..... 78.8 Cigarettes ..... 5.3 Hookah ..... 1.5 Chilum 0.8	132	Controls individually matched as for U.S.A. data above: *Percent* Nonsmokers ..... 30.3 Bidis ..... 62.1 Cigarettes ..... 4.5 Hookah ..... 0.8 Chilum 2.3	Interviews for smoking and medical histories.
Schwartz et al., 1957, France (*248*).	M.	121	Patients hospitalized from 1954 through 1956 with laryngeal cancer, in Paris and other large cities: *Percent* Smokers ..... 96 Inhalers ..... 58 Roll their own cigarettes 44	242	Same time and sources; patients hospitalized for non-cancerous conditions or trauma: *Percent* Smokers ($p<0.05$) ..... 84 Inhalers ($p<0.05$) ..... 47 Roll their own cigarettes 31	Cases and controls individually matched within institutions; each member of a set questioned by the same trained lay interviewer.

TABLE A21.—*Outline of retrospective studies of tobacco use and cancer of the larynx (cont.)*

Author, year, country, reference	Cases			Controls		Collection of data
	Sex	Number	Method of selection	Number	Method of selection	
Wynder et al., 1957, Sweden (*322*).	M.	60	Patients at Radiumhemmet with squamous-cell cancer of larynx, from 1952 through 1955:	271	Patients from same source and time, with cancer other than squamous-cell of larynx:	By trained lay interviewers in hospital.
			Percent		*Percent*	
			Nonsmokers 5		Nonsmokers 24	
			Cigarettes 47		Cigarettes 36	
			Cigars 17		Cigars 9	
			Pipes 16		Pipes 16	
			Mixed 17		Mixed 13	
Wynder et al., 1958, Cuba (*325*).	M. F.	142 32	Clinic patients in Havana during 1956-57, with histologically diagnosed epidermoid cancer of larynx.	220 214	Same source and time; apparently patients with cancers other than larynx, lung, or oral cavity, matched for age:	Interview of patients in clinic.
			Percent *Male* *Female*		*Percent* *Male* *Female*	
			Nonsmokers 1 13		Nonsmokers 16 66	
			Cigarettes 62 72		Cigarettes 45 27	
			Cigars 20 6		Cigars 22 6	
			Pipes ..... 1 ..		Pipes ..... 1 ..	
			Mixed 16 9		Mixed ..... 16 ..	
Dutta-Choudhuri et al., 1959, India (*86*).	M-F	582	Patients in Calcutta cancer hospital during 1950-54, with laryngeal tumor diagnosed and confirmed by biopsy or smear:	288	Not specified	Tobacco histories obtained during 1951-54, apparently by interviewer.
			Percent		*Percent*	
			Nonusers 14.1		Nonusers 41.7	
			Cigarettes or bidi 77.8		Cigarettes or bidi 52.1	
			Chew 3.1		Chew 3.8	
			Both 5.0		Both 2.4	

TABLE A21.—*Outline of retrospective studies of tobacco use and cancer of the larynx (cont.)*

Author, year, country, reference	Cases			Controls		Collection of data
	Sex	Number	Method of selection	Number	Method of selection	
Staszewski, 1960, Poland (259).	M. F.	207 13	Patients admitted to chronic disease hospital during 1957 and 1958 with histologically confirmed squamous-cell carcinoma of the larynx: *Percent* Nonsmokers ..... 0.5 Cigarettes only ..... 87.9 Pipes and/or cigars ..... 1.9 "Heavy smokers" ..... 88.4 Inhalers ..... 96.1 Female smokers 30.8	912 1,813	Patients admitted during 1957 and 1958 to chronic disease center for cancerous and noncancerous conditions presumably not related to tobacco consumption: *Percent* Nonsmokers ..... 17.3 Cigarettes only ..... 60.5 Pipes and/or cigars ..... 11.1 "Heavy smokers" ..... 49.0 Inhalers ..... 66.8 Female smokers 8.4	Author interviewed patients suspected of lung cancer for smoking history and background.
Rozenbilds, 1967, Australia (229).	M. F.	191 21	Patients admitted to 3 major hospitals with cancer of larynx and hypopharynx: *Percent* Nonsmokers ..... 8 Smokers ..... 92 Heavy smokers 30		No controls.	Patient interviews.
Terracol et al., 1967, France (274).	M.	961	Private service and clinic patients of ENT hospital: *Percent* Nonsmokers ..... 12.1 Smokers 87.9		No controls.	Patient interviews.
Svoboda, 1968, Czechoslovakia (271).	M. F.	205 10	Patients admitted to a regional hospital over a period of 6 years all confirmed histologically: *Percent* Nonsmokers ..... 2.93 Cigarettes ..... 94.63 Pipes 2.44	320	Male controls *Percent* Nonsmokers ..... 22.0 Cigarettes (approximately) . 71.0 Pipes (approximately) 7.0	Cases: patient interviews. Controls: not stated.

TABLE A22.—*Summary of results of retrospective studies of tobacco use and cancer of the larynx*

(Figures in parentheses represent ratios based on less than 5 case nonsmokers.)

Investigator reference	Relative risk ratio [1] all smokers to nonsmokers
Schrek et al., U.S.A. (*246*)	2.0
Valko, Czechoslavakia (*292*)	3.5
Sadowsky et al., U.S.A. (*232*)	3.7
Blumlein, Germany (*26*)	27.5
Wynder et al., U.S.A. (*314*)	23.6
Wynder et al., India (*312*)	3.1
Schwartz et al., France (*254*)	4.6
Wynder et al., Sweden (*322*)	6.0
Wynder et al., Cuba (*325*)	(18.9) (males only)
Datta-Choudhuri et al., India (*86*)	4.3
Stazewski, Poland (*259*)	(40.0) (males only)
Svoboda, Czechoslavakia (*271*)	8.3

[1] Computed according to method of Cornfield, J. (*61*).

TABLE A23.—*Number and percent distribution by relative frequency of atypical nuclei among true vocal cord cells, of men classified by smoking category*

(100 percent atypical cells defined as carcinoma)

Percent atypical nuclei	Never smoked regularly		Ex-cigarette smokers		Cigar/pipe smokers		Current cigarette smokers					
							Less than 1 pack a day		1-2 packs a day		2 or more packs a day	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Total	88	100.0	116	100.0	94	100.0	125	100.0	329	100.0	190	100.0
None	66	75.0	86	74.1	1	1.1	1	.8	0	—	0	—
Less than 50	8	9.1	14	12.1	4	4.3	25	20.0	4	1.2	0	—
50-59	10	11.4	13	11.2	50	53.0	54	43.2	87	26.4	29	15.3
60-69	4	4.5	1	.9	23	24.5	21	16.8	116	35.3	75	39.4
70-79	0	--	2	1.7	9	9.6	9	7.2	44	13.4	38	20.0
80-89	0	—	0	—	2	2.1	2	1.6	19	5.8	11	5.8
90-99	0	—	0	—	1	1.1	0	--	5	1.5	0	--
100:												
Carcinoma in situ	0	—	0	—	3	3.2	13	10.4	52	15.8	35	18.4
Invasive carcinoma	0	--	0	--	1	1.1	0	--	2	.6	2	1.1

Source: Auerbach, O. et al. (9).

TABLE A24.—*Number and percent distribution, by highest number of cell rows in the basal layer of the true vocal cord, of men classified by smoking category*

Number of cell rows	Never smoked regularly		Ex-cigarette smokers		Cigar/pipe smokers		Current cigarette smokers					
							Less than 1 pack a day		1–2 packs a day		2 or more packs a day	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Total	88	100.0	116	100.0	94	100.0	125	100.0	329	100.0	190	100.0
Less than 5 cell rows	30	34.1	7	6.0	4	4.3	3	2.4	1	0.3	0	...
5 cell rows	29	33.0	27	23.3	20	21.3	27	21.6	38	11.6	20	10.6
6 cell rows	8	9.1	15	12.9	15	6.0	25	20.0	51	15.4	24	12.6
7 cell rows	6	6.8	12	10.3	18	19.1	12	9.6	38	11.6	19	10.0
8 cell rows	8	9.1	14	12.1	9	9.6	13	10.4	30	9.1	23	12.1
9 cell rows	1	1.1	7	6.0	7	7.4	6	4.8	26	7.9	14	7.4
10 or more cell rows	6	6.8	34	29.4	21	22.3	39	31.2	145	44.1	90	47.4

Source: Auerbach, O. et al. (9).

TABLE A28.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity*

(Data obtained from patient interview and other sources)

Author, year, country, reference	Sex	Cases: Number	Cases: Method of selection	Controls: Number	Controls: Method of selection	Comments
Borders, 1920, U.S.A. (*43*).	M. F.	526 11	Series of clinic patients with epithelioma of the lip: *Percent* Tobacco users ..... 80.5 Smokers ..... 75.1 Cigarettes ..... 0.9 Chewers ..... 24.0 Pipes ..... 59.0 Cigars 38.5	500	Series of clinic patients without epithelioma of the lip: *Percent* Tobacco users ..... 78.6 Smokers ..... 75.2 Cigarettes ..... 44.4 Chewers ..... 13.4 Pipes ..... 28.6 Cigars 44.0	
Ebenius, 1943, Sweden (*87*).	M. F.	439 33	Clinic patients with cancer of the lip: *Percent* *Male* *Female* Tobacco users ..... 79.7 — Tobacco users (all pipes) ..... — 57.6 Pipes ..... 61.8 — Chew or use snuff .... 47.4 — Cigars and cigarettes .. 12.9 —	300	Not defined. *Percent* *Male* *Female* Tobacco users ..... 68.7 — Tobacco users ..... — †1–2 Pipes ..... 22.9 — Chew or use snuff ..... 60.7 — Cigars and cigarettes .. 32.5 —	† Estimate of prevalence of use.
Levin et al., 1950, U.S.A. (*169*).	M.	143	Cancer Institute patients with cancer of the lip: *Percent* Smokers ..... 84.5 Cigarettes ..... 45.3 Pipes ..... 48.1 Cigars 26.5	51	Cancer Institute patients with non-cancer diseases of same site: *Percent* Smokers ..... 74.0 Cigarettes ..... 43.0 Pipes ..... 30.7 Cigars 34.9	

TABLE A28.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity* (cont.)

(Data obtained from patient interview and other sources)

Author, year, country, reference	Cases			Controls		Comments
	Sex	Number	Method of selection	Number	Method of selection	
Mills and Porter, 1950, U.S.A. (*186*).	M.	124	Deaths from cancer of oral cavity in Cincinnati and Detroit, 1940-45 and 1942-46 respectively: *Percent* Cigarettes only ..... 35.5 Pipes, cigars, or combinations 54.8	185	Sample of population of Columbus, Ohio, in same proportion of color, sex, and age as in cases: *Percent* Cigarettes only ..... 32.4 Pipes, cigars, or combinations 29.7	
Moore et al., 1953, U.S.A. (*194*).	M.	112	Patients over 50 years old since 1951 with cancer of oral cavity: *Percent* Chewers ..... 58.0 Pipes ..... 42.0 Cigars and cigarettes 38.4	38	Patients of same age groups with benign oral lesions or benign surgical conditions: *Percent* Chewers ..... 31.6 Pipes ..... 47.4 Cigars and cigarettes 52.6	
Sadowsky et al., 1953, U.S.A. (*332*).	M.	1,136	Hospital patients with lip, oral, and pharyngeal cancer, 1938-44: *Percent* Cigarettes only ..... 42.3 Cigars only ..... 4.0 Pipes only ..... 17.8 Mixed 28.2	615	Patients with illness other than cancer: *Percent* Cigarettes only ..... 53.3 Cigars only ..... 3.4 Pipes only ..... 7.0 Mixed 23.1	
Sanghvi et al., 1955, India (*241*).	M. F.	657 81	Hospital patients with cancer of oral cavity and pharynx: *Percent* *Male* *Female* Smoke and chew ..... 38.8 3.7 Smoke only ..... 46.7 6.2 Chew only ..... 11.7 64.2 Neither 2.7 25.9	288 112	Hospital patients with diseases other than cancer: *Percent* *Male* *Female* Smoke and chew ..... 24.0 Smoke only ..... 50.0 6.3 Chew only ..... 8.7 23.2 Neither 17.3 70.5	Smoking is of bidis among both cases and controls.

TABLE A28.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity (cont.)*

(Data obtained from patient interview and other sources)

Author, year, country, reference	Sex	Cases		Controls		Comments
		Number	Method of selection	Number	Method of selection	
Ledermann, 1955, France (*162*).	M.	240	Patients with cancer of oral cavity and pharynx: *Percent* Nonsmokers ..... 4.6 >20 cigarettes per day 23.4	62	Patients with cancer of skin, bone, and muscle: *Percent* Nonsmokers ..... 17.2 >20 cigarettes per day 18.6	Differences between cases and controls for both high and low alcohol intake are insignificant when smoking is controlled.
Wynder et al., 1957, U.S.A. (*313*).	M. F.	543 116	Patients with cancer of oral cavity: *Percent* *Male* *Female* Nonsmokers ..... 3 47 Cigars ..... 20 — Pipes ..... 11 — Mixed ..... 8 — Chew ..... 17 — Cigarettes ..... 57 53 >35 cigarettes per day ..... 20 — >16 cigarettes per day 34	207 232	Patients with cancer of other sites and benign diseases: *Percent* *Male* *Female* Nonsmokers ..... 10 70 Cigars ..... 13 — Pipes ..... 6 — Mixed ..... 8 — Chew ..... 8 — Cigarettes ..... 63 30 >35 cigarettes per day ..... 17 — >16 cigarettes per day 11	
Schwartz et al., 1957, France (*248*).	M.	332	Hospital patients with cancer of oral cavity and pharynx: *Percent* Nonsmokers ..... 16.4 Cigarettes only ..... 62.7 Pipes only 3.3	608	Hospital patients with non-cancer illness and accident cases, matched by age: *Percent* Nonsmokers ..... 23.4 Cigarettes only ..... 58.2 Pipes only 3.0	

TABLE A28.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity (cont.)*

(Data obtained from patient interview and other sources)

Author, year, country, reference	Sex	Cases		Controls		Comments
		Number	Method of selection	Number	Method of selection	
Wynder et al., 1957, Cuba (*325*).	M. F.	178 34	Hospital clinic patients with cancer of oral cavity and pharynx: *Percent* *Male* *Female* Nonsmokers ..... 4 24 Cigarettes predominantly ..... 45 62 Cigars predominantly . 33 12	220 214	Patients in same clinics with non-malignant conditions, matched by sex and age: *Percent* *Male* *Female* Nonsmokers ..... 16 66 Cigarettes predominantly ..... 45 27 Cigars predominantly . 22 6	
Wynder et al., 1957, Sweden (*322*).	M.	115	Male patients with cancer of oral cavity and pharynx: *Percent* Cigarettes ..... 36.5 Cigars ..... 13.0 Pipes ..... 12.2 Mixed 15.7	115	Male patients in same hospital with cancer of sites other than oral, pharynx, larynx, lung, esophagus, breast: *Percent* Cigarettes ..... 36 Cigars ..... 9 Pipes ..... 16 Mixed 13	Alcohol data significant only for hypopharynx.
Peacock et al., 1960, U.S.A. (*210*).	M. F.	25 20	Hospital patients with oral cancer: *Percent* Chewed or used snuff over 20 years (all patients) 55.6	74 72	Patients in same hospital without oral cancer and 117 male and 100 female out-patients, randomly selected. 32.6 percent of first group, and 43.3 percent of second group chewed or used snuff over 20 years.	
Staszewski, 1960, Poland (*259*).	M.	383	Male patients with oral cancer: *Percent* Nonsmokers ..... 5.7 "Heavy" smoking index ..... 72.8 Cigarettes only ..... 72.3 Pipes and/or cigars 12.8	912	Male patients with other cancerous and non-cancerous conditions: *Percent* Nonsmokers ..... 17.3 "Heavy" smoking index ..... 49.0 Cigarettes only ..... 60.5 Pipes and/or cigars 11.1	

TABLE A28.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity (cont.)*

(Data obtained from patient interview and other sources)

Author, year, country, reference	Sex	Cases: Number	Cases: Method of selection	Controls: Number	Controls: Method of selection	Comments
Vogler et al., 1962, U.S.A. (*298*).	M. F.	188 92	Clinic patients with cancer of lip and oral cavity: *Percent* Male / Female Chewers ..... †32.9 / — Excessive chewers .... 22.9 / — Snuff dippers ..... — / 72.0 Excessive snuff dippers ..... — / 41.3 Tobacco users ..... 90.0 / 90.0	521 1,064	Patients of same clinic with other cancer or non-malignant conditions: *Percent* Male / Female Snuff dippers .... †6.1 Tobacco users ..... 56.0 / 56.0	† Due to varying tabular treatment of data, percentages of tobacco users are not all based on the same number of cases.
Vincent and Marchetta, 1963, U.S.A. (*297*).	M. F.	66 16	Successive patients with lesions of buccal cavity and oropharynx: *Percent* Oral Cavity / Oro-pharynx Males: Nonsmokers ..... 3.0 / — <20 cigarettes per day ..... 18.3 / 15.1 >20 cigarettes per day ..... 78.7 / 84.9 Females: Nonsmokers ..... 55.5 / 28.6 <20 cigarettes per day ..... — / — >20 cigarettes per day ..... 44.5 / 71.4	100 50	Successive patients attending gastrointestinal clinic, age-matched; *Percent* 27.0 24.0 49.0 82.0 8.0 10.0	Male patients used considerably more alcohol than male controls. Data refers to all forms of smoking expressed as cigarette equivalents. Cigarette equivalents: 1 cigar = 5 cigarettes 1 pipe = 2 cigarettes † BN=Betel nut.

TABLE A28.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity (cont.)*

(Data obtained from patient interview and other sources)

Author, year, country, reference	Sex	Cases: Number	Cases: Method of selection	Controls: Number	Controls: Method of selection	Comments
Shanta and Krishnamurthi, 1964, India (*256*).	M. F.	552 206	Patients with oral and pharyngeal cancer (unsure of confirmation):	300 100	Controls residing in same area matched for age, sex, and class:	
			Males: — *Lip*; *Buccal mucosa*; *Anterior tongue*; *Posterior tongue*; *Pharynx*; *Males* (Percent)			
			No tobacco habit .... — 2.0 7.2 2.0 5.3 39.1			
			Smokers 50.0 45.7 66.6 75.0 72.8 52.7			
			Number of cases .... (12) (203) (69) (48) (130) (300)			
			Females: — *Females*			
			No tobacco habit .... 14.3 11.0 33.3 — 40.0 88.8			
			Smokers ..... — 4.7 5.5 — 8.8 —			
			Number of cases .... (7) (162) (18) (4) (25) (100)			
Wahi et al., 1965, India (*302*).	M. F.	589 232	Patients with oral and pharyngeal carcinoma:	589 232	Patients matched for age, sex, religion, and social class.	
					Percent	
			Nonsmokers 9.62		66.5	
			Smokers 17.05		21.2	
			Chewers (Betel nut) 35.44		5.9	
			Both 37.88		6.4	
Hirayama, 1966, Central and South East Asia (*124*).	M. F.	369 176	Patients with oral and pharyngeal carcinoma:	277 163	Patients with other (unspecified) diseases:	Found only a suggestive association between alcohol-drinking and oral cancer in non-chewers only. † BN-Betel nut.
					Percent	
					Male *Female*	
			Nonusers 1.6 2.5		17.0 33.0	
			Smokers 17.1 2.5		23.8 1.2	
			Smokers, †BN and tobacco chewers 46.7 6.6		24.9 1.8	

TABLE A28.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity (cont.)*

(Data obtained from patient interview and other sources)

Author, year, country, reference	Cases			Controls		Comments
	Sex	Number	Method of selection	Number	Method of selection	
Keller, 1967, U.S.A. (*140*).	M	408	Patients with squamous cell carcinoma of oral cavity and oropharynx confirmed histologically. Three New York City VA Hospitals 1953-63:	408	Next male patient admitted to same hospital within 5 year age range.	Excessive alcohol consumption noted for cases involving floor, mesopharynx, and tongue. Findings indicate the association of heavy drinking with cancer independent of the amount of tobacco used.
			Percent		*Percent*	
			Nonusers 5.1		14.2	
			Cigarettes 68.6		56.4 ($p<0.0001$)	
			Pipe only 4.0		2.9	
			Cigar only 6.9		6.1	
Martinez, 1969, Puerto Rico (*185*).	M. F.	38	Patients with epidermoid carcinoma of oral cavity and pharynx:	345 114	116 male and 38 female hospital or clinic patients without cancer; 330 male and 76 female residents of same region, age and sex matched.	Cases found to consume more alcoholic beverages than controls.
			Percent		*Percent*	
			Nonsmokers 13.7		19.2	
			Heavy tobacco users 24.8		12.2 ($p<0.0001$)	
Keller, 1970, U.S.A. (*141*).	M.	304	Patients with primary basal or squamous cell carcinoma of lip:	304	Patients from same hospital matched for age and race.	
			Percent		*Percent*	
			Nonsmokers 7.3		16.6 ($p<0.001$)	
			Cigarettes only 60.2		52.8	
			Pipe only 6.0		3.4	
			Pipe, other 6.3		0.4 ($p<0.01$)	

TABLE A28a.—*Summary of results of retrospective studies of smoking by type and oral cancer of detailed sites*

Author reference	Cigarettes	Cigarettes and cigars	Bidis	Pipes only	Pipes and other forms	Cigars only	Tobacco chewing	Betel nut chewing	Miscellaneous
Broders (*43*)	Lip (−)			Lip (+)		Lip (−)	Lip (+)		
Ebenius (*87*)		Lip (−)		Lip (+)			Lip (−)		
Levin et al. (*169*)	Lip (−)			Lip (+)		Lip (*)			
Mills and Porter (*186*)	Oral (*)								Pipes and cigars combined—oral (+).
Moore et al. (*193*)		Lip, mouth (−).		Lip, mouth (−)			Lip, mouth (+)		Snuff—lip, mouth (+).
Sadowsky et al. (*232*)	Lip, tongue, other oral, pharynx (−)			Lip, tongue, other oral (+)		Tongue, other oral (*)			
Sanghvi et al. (*241*)			Oral (+)				Oral (+)		If smokers and chewers—base of tongue, hypopharynx (+).
Lederman (*162*)	Oral (+)								
Wynder et al. (*313*)	Floor of mouth Male (*) Female (+)			Each site except tongue (+)		Each site (+)	Gingiva, lip (*)		
Schwartz et al. (*243*)		Pharynx (+)		Oral (−)					

TABLE A28a.—*Summary of results of retrospective studies of smoking by type and oral cancer of detailed sites (cont.)*

Author reference	Cigarettes	Cigarettes and cigars	Bidis	Pipes only	Pipes and other forms	Cigars only	Tobacco chewing	Betel nut chewing	Miscellaneous
Wynder et al. (325)	Oral and pharynx, Male (−) Female (+)	.....	.....	.....	.....	Oral and pharynx, Male (+), Female (+)	.....	.....	
Wynder et al. (325)	Pharynx (+), other sites (−).	.....	.....	.....	.....	Tongue, gingiva, pharynx (+).	.....	.....	Pipes and cigars combined—tongue (+).
Peacock et al. (210)	.....	.....	.....	.....	.....	.....	Oral (+)[1]	.....	Snuff—oral (+)[1]
Staszewski (259)	Lip, oral cavity (+)	.....	.....	.....	.....	.....	.....	.....	Pipes and cigars combined—lip, oral cavity (*).
Vogler et al. (293)	.....	.....	.....	.....	.....	.....	.....	.....	All forms combined (+), Female (+) Snuff—lip and buccal cavity in both cases.
Vincent and Marchetta (297)	.....	.....	.....	.....	.....	.....	.....	.....	All forms combined—oral (+), pharynx (+).
Shanta and Krishnamurthi (256	.....	.....	.....	.....	.....	.....	.....	Lip, buccal mucosa (+)	All smoking types—pharynx (+), post tongue (+). All forms combined—lip, oral cavity, pharynx (+).

TABLE A28a.—*Summary of results of retrospective studies of smoking by type and oral cancer of detailed sites (cont.)*

Author reference	Cigarettes	Cigarettes and cigars	Bidis	Pipes only	Pipes and other forms	Cigars only	Tobacco chewing	Betel nut chewing	Miscellaneous
Wahi et al. (*302*)	Anterior tongue and buccal mucosa, Males (+)							Anterior tongue and buccal mucosa, Males (+)	All forms combined—all sites (+).
Hirayama (*124*)				All sites (−)		All sites (−)	All sites (−)		All forms combined—base of tongue (+), oropharynx (+). Smoking only combined—buccal mucosa (+).
Keller (*140*)	All sites (+)			All sites (−)		All sites (−)			All types smoking combined, heavy—floor of mouth and tongue (+).
Martinez (*185*)	Oral cavity, pharynx (+)								All types of smoking, heavy, combined—oral cavity (+), pharynx (+).
Keller (*141*)	Lip (−)				Lip (+)	Lip (−)			All types of smoking combined—lip (+).

[1] Only in individuals of low economic status and over 60 years old.

Symbols: (+) = significant association.
(−) = association absent or not significant.
(°) = association of doubtful significance.

TABLE A29.—*Experimental studies concerning oral carcinogenesis*

Author, year, country, reference	Animal and strain	A. Method. B. Frequency and/or duration. C. Material.	Results
Kreshover, 1952, U.S.A. (*152*).	78 Swiss and C57 mice.	A. Painting of lower lip mucocutaneous region. B. 10 times in 76 days. C. Cigarette smoke "concentrate".	No macroscopic or microscopic changes in controls or experimental animals.
Salley, 1954, U.S.A. (*235*).	36 Syrian hamsters.	A. Painting of cheek pouch. B. 3 per week for 16 weeks. C. Benz(a)pyrene in acetone or benzene.	Treatment: — *Number of survivors*: Acetone solvent 5; Benzene solvent 4. *Number with benign tumors*: Acetone solvent 1; Benzene solvent —. *Number with carcinoma*: Acetone solvent 2; Benzene solvent —.
Holsti and Ermala, 1955, Finland (*130*).	60 Albino mice (40 controls).	A. Painting of lips and oral cavity. B. 140 times in 12 months. C. Tobacco "tar".	No oral or labial changes seen in controls or experimental animals.
Moore and Miller, 1958, U.S.A. (*192*).	80 Syrian Golden hamsters.	A. Material soaked onto wad and secured in cheek pouch. B. Wads replaced 8 times in 2 years. C. Smoke condensate Benz(a)pyrene.	Treatment: — *Original number*: Controls 30; Smoke condensate 80; Benz(a)pyrene 20. *Surviving over 1 year*: Controls 28; Smoke condensate 56; Benz(a)pyrene 16. *Number tumors*: Controls ..; Smoke condensate ..; Benz(a)pyrene .. *Inflammation and basal cell hyperplasia*: Controls 4; Smoke condensate 32; Benz(a)pyrene 9.
Guerin, 1959, France (*108*).	Strain IC and strain W rat.	A. Chamber inhalation of tobacco smoke. B. Daily (?). C. Up to 6½ months.	*Original number*: Controls 40; Experimental 100. *Survivors*: Controls 39; Experimental 68. *Buccal tumors*: Controls 0/39; Experimental 5/68 (3/5 definite epithelioma)

TABLE A29.—*Experimental studies concerning oral carcinogenesis (cont.)*

Author, year, country, reference	Animal and strain	A. Method. B. Frequency and/or duration. C. Material.	Results
Peacock et al., 1960, U.S.A. (210).	124 Syrian Golden hamsters.	A. Packing of cheek pouch. B. 1 year. C. Snuff, Tobacco, Bland material.	No tumors noted in any of the 42 animals surviving over 1 year.
Dunham and Herrold, 1962, U.S.A. (84).	Syrian Golden hamsters.	A. Packing of cheek pouch. B. Normal lifespan or 5–30 months. C. Betel quid ingredients 7-12 dimethylbenz(a)-anthracene (DMBA), Methylcholanthrene (MCA) in beeswax pellets.	Treatment: Betel quid — Original number 375 — Survivors 90% over 1 year — Hyperplasia and/or inflammation 19 — Malignant pouch tumors — Treatment: DMBA and MCA — Original number 71 — Survivors 56/71 over 5–30 months — Hyperplasia and/or inflammation — — Malignant pouch tumors 23/56
Moore and Christopherson, 1962, U.S.A. (191).	Albino hamster exteriorized oral pouch.	A. Painting oral mucosa. B. 3 per week for 683 days. C. Cigarette smoke condensate. DMBA in 0.5% petrolatum.	Treatment: — Animals with lesions (time) Controls — 0/18 (at 392 days). Smoke condensate — 0/20 (at 337 days) (10 showed hyperkeratosis). DMBA — 14/21 microscopic cancers (at 90 days) (invasive squamous cancer originating in the skin at the edge of the pouch).
Salley, 1963, U.S.A. (239).	CAF_1 strain mice.	A. Ultraviolet light exposure to and painting of lips. B. 3 per week for 98 weeks. C. B(a)P in acetone Cigarette smoke UV light.	Treatment: Ultraviolet light and cigarette smoke — Number 40 — Duration weeks 94 — Tumors — B(a)P and UV light — Number 40 — Duration weeks 48 — Tumors — UV light — Number 40 — Duration weeks 94 — Tumors — B(a)P — Number 40 — Duration weeks 48 — Tumors —

TABLE A29.—*Experimental studies concerning oral carcinogenesis (cont.)*

Author, year, country, reference	Animal and strain	A. Method. B. Frequency and/or duration. C. Material.	Results				
	Hamsters	A. Application to check pouch.	Treatment:	*Original Number*	*Survivors*	*Duration*	*Lesions*
		B. See results.	Cigarettes 5 per week	70	55	64	—
		C. See results.	DMBA once	13	6	128	2 hyperplasia
			Croton oil 3 per week	10	10	30	—
			DMBA once and cigarettes 5 per week	30	28	81	12 hyperplasia 4 dyskeratosis 1 carcinoma
			DMBA once then croton oil 5 per week	29	27	81	7 hyperplasia 6 dyskeratosis 3 carcinoma
Bock et al., 1964, U.S.A. (*90*).	ICR Swiss mice.	A. Painting mouse skin.					
		B. See results 36 weeks.			*Tobacco equivalent (cigarettes/daily)*		*Number tumors/number mice with tumors (small papillomas)*
		C. Various extracts of unburned tobacco DMBA.	Treatment:				
			DMBA once then:				
			Acetone benzene extract		2.5		16/7
			Concentrated $Ba(OH)_2$ extract		0.5		18/8
			Diluted $Ba(OH)_2$ extract		0.5		6/2
			DMBA only		—		—
			Acetone benzene extract		2.5		—
			Concentracted $Ba(OH)_2$ extract		0.5		—
			Diluted $Ba(OH)_2$ extract		0.5		—
			None		—		—

TABLE A29.—*Experimental studies concerning oral carcinogenesis (cont.)*

Author, year, country, reference	Animal and strain	A. Method. B. Frequency and/or duration. C. Material.	Results			
				Original number	*Percent at 13 months with* Papilloma	Cancer
Protzel et al., 1964, U.S.A. (*218*).	Swiss Webster mice with some having liver damage induced either by CCl4 or ethyl alcohol.	A. Swabbing of labial mucosa. B. Up to 13 months. C. B(a)P in acetone.	Alcohol and CCl_4 treated	40	74	46
			Alcohol treated	40	84	50
			CCl_4 treated	40	90	40
			No toxin	40	42	15
Reddy and Anguli, 1967, India (*219*).	Swiss female mice.	A. Intravaginal instillation. B. Daily for 324–380 days. C. "Pan" mixture of areca nuts, lime, and chewing tobacco.	*Original number*: 60	*Survivors*: 40	*Lesions*: 3/40 raised papillomatous malignant growths 4/40 possible carcinoma-in-situ.	
Elzay, 1969, U.S.A. (*90*).	Syrian Golden hamsters.	A. Application to cheek pouch. B. Daily for 200 days. C. See results.	Treatment:	*Original number*	*Mortality rate*	*Number animals*	*Percent with tumors*	*Percent with cancer*
			DMBA Alcohol Smoke	29	41.0	17	100.0	50.0
			DMBA Alcohol	29	66.0	10	60.0	40.0
			DMBA ..... Smoke	29	42.0	14	100.0	70.0
			DMBA	29	48.0	15	100.0	88.0
			..... Alcohol Smoke	29	42.0	14	—	—
			.... Smoke	29	42.0	14	—	—

TABLE A31.—*Summary of methods used in retrospective studies of tobacco use and cancer of the esophagus*

Author, year, country, reference	Cases			Controls		Collection of data
	Sex	Number	Method of selection	Number	Method of selection	
Sadowsky et al., 1953, U.S.A. (238).	M.	104	White patients admitted during 1938-43 to selected hospitals in New York City, Missouri, New Orleans, and Chicago.	616	White patients with illnesses other than cancer admitted to same group of hospitals during same period.	Obtained by 4 specially trained lay interviewers. 242 records out of a total of 2,847 excluded because of incomplete or questionable smoking histories.
Sanghvi et al., 1955, India (241).	M.	73	Consecutive clinic admissions to Tata memorial Hospital, Bombay.	288	Consecutive clinic admissions of patients without cancer.	By means of "detailed questionary." No other details given.
				107	Consecutive admissions of patients with cancers other than intraoral or esophagus.	
Wynder et al., 1957, Sweden (322).	M.	39	Patients admitted to Radiumhemmet, Stockholm, during 1952-55.	115	Patients admitted to same hospital with cancer of skin, head and neck region other than squamous cell cancer, leukemia, colon, and other sites. No matching.	
	F.	35		166		
Staszewski, 1960, Poland (260).	M.	24	Patients admitted to Oncological Institute during 1957-59.	912	Other patients sent to Institute with symptoms probably not etiologically connected either with smoking or with diseases of esophagus, stomach or duodenum.	No details given on method of data collection. No age adjustment or matching. Average age of cancer patients, 60.5; controls, 53.

TABLE A31.—*Summary of methods used in retrospective studies of tobacco use and cancer of the esophagus (cont.)*

Author, year, country, reference	Cases			Controls		Collection of data
	Sex	Number	Method of selection	Number	Method of selection	
Schwartz et al., 1961, France (*249*).	M.	362	Admissions to hospitals in Paris and a few large provincial cities since 1954.	362	Healthy individuals admitted to same hospital because of work or traffic accidents—matched by 5 year age group and time of admission.	Interviewed by team of specially trained interviewers who interviewed the largest proportion possible of all cancer patients. Cases and matched controls interviewed by same person.
Wynder and Bross, 1961, U.S.A. (*310*).	M.	150	Cancer patients seen in Memorial Hospital, New York City, and Kingsbridge and Brooklyn VA Hospitals during 1950–59 (86% white).	150	Patients seen in same hospitals during same time period with other tumors. 64%-malignant tumor; 36%-benign conditions. Matched by age with cancer patients.	Data collected by trained interviewers.
	F.	37	Same hospitals and same time period as male patients (86% white).	37	Same as with regard to male controls. 43% had malignant and 57% benign tumors.	
Wynder and Bross, 1961, India (*310*).	M. F.	67 27	Admitted to Tata Memorial Hospital Bombay.	134	Patients with other forms of cancer except for oral cavity and lungs; as well as various benign diseases.	Interviewed by one person. 10% of male and 4% of female cancer cases histologically confirmed.
Takano et al., 1968, Japan (*272*).	M. F.	167 33	Patients with esophageal cancer.	167 33	Patients with cancerous and non-cancerous diseases of non-digestive organs.	Interviews at various hospitals. Cases and controls age-matched.

TABLE A31.—*Summary of methods used in retrospective studies of tobacco use and cancer of the esophagus (cont.)*

Author, year, country, reference	Cases			Controls		
	Sex	Number	Method of selection	Number	Method of selection	Collection of data
Bradshaw and Schonland, 1969, South Africa (*41*).	M.	98	Patients with esophageal cancer.	341	Patients with non-malignant disease.	Hospital interviews by trained African social workers.
Martinez, 1969, Puerto Rico (*183*).	M. F.	120 59	Patients with confirmed epidermoid esophageal cancer diagnosed in 1966.	360 177	120 male, 59 female patients in same hospital with non-cancerous diagnoses. 240 male, 118 female members from same community.	Interviews by trained personnel.

TABLE A31a.—*Summary of results of retrospective studies of tobacco use and cancer of the esophagus*

Author, year, country, reference		Percent nonsmokers		Percent heavy smokers		Percent inhalers among smokers		Relative risk ratio. All smokers to nonsmokers	
		Cases	Controls	Cases	Controls	Cases	Controls	All smokers	Heavy smokers
Sadowsky et al., 1953, U.S.A. (*233*).		3.8	13.2	—	—	—	—	4.0	—
Sangvhi et al, 1955, India (*241*).		5.5	17.3	*Average number of bidis smoked* 15.3	14.1	—	—	3.6	—
Wynder et al., 1957, Sweden (*322*).	M	13.0	24.0						
	F	(about) 85.0	(about) 92.0	—	—	—	—	2.1	—
				—	—	—	—	2.0	—
Staszewski, 1960, Poland (*260*).		—	18.0	95.8	59.0	87.5	80.0	—	—
Schwartz et al., 1961, France (*249*).		3.0	17.0	*Total amount smoked daily (cigarettes)* 16.8	10.0	39.0	38.0	6.6	—
Wynder and Bross, 1961, U.S.A. and India (*310*).	American males	5.0	15.0	48.0	33.0	—	—	3.4	4.4
	American females	41.0	78.0	27.0	16.0	—	—	5.1	3.2
	Indian males	13.0	28.0	—	—	—	—	2.6	—
	Indian females	78.0	94.0	—	—	—	—	4.5	—
Takano et al., 1963, Japan (*272*).		17.0	23.0	—	—	—	—	1.3	—
Bradshaw and Schonland, 1969, South Africa (*41*).		15.3	31.7	31.6	5.9	—	—	2.6	11.1
Martinez, 1969, Puerto Rico (*183*).		14.0	23.6	17.9	8.6	—	—	1.8	3.5

TABLE A32.—*Atypical nuclei in basal cells of epithelium of esophagus of males, by smoking habits and age*

Atypical nuclei	Never smoked regularly		Current Cigarettes		Ex-cigarettes		Pipe, cigar		Other	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
A. All men:										
Number men	91	—	779	—	181	—	89	—	62	—
Total sections[1]	787	100.0	6,752	100.0	1,586	100.0	766	100.0	522	100.0
No atypical nuclei	733	93.1	167	2.5	770	48.5	53	6.9	195	37.4
Some but <60 percent atypical	52	6.6	5,389	79.8	765	48.3	688	89.8	317	60.7
60 percent or more atypical	2	0.3	1,196	17.7	51	3.2	25	3.3	10	1.9
B. Men under age 50:										
Number men	26	—	236	—	28	—	9	—	7	—
Total sections	223	100.0	2,059	100.0	258	100.0	77	100.0	53	100.0
No atypical nuclei	190	85.2	71	3.4	56	21.7	1	1.3	4	7.5
Some but <60 percent atypical	33	14.8	1,853	90.0	195	75.6	74	96.1	46	86.8
60 percent or more atypical	—	—	135	6.6	7	2.7	2	2.6	3	5.7
C. Men aged 50-69:										
Number men	44	—	445	—	109	—	38	—	31	—
Total sections	379	100.0	3,853	100.0	953	100.0	310	100.0	256	100.0
No atypical nuclei	373	98.4	83	2.2	461	48.4	37	11.9	74	28.9
Some but <60 percent atypical	4	1.1	2,915	75.6	452	47.4	261	84.2	178	69.5
60 percent or more atypical	2	0.5	855	22.2	40	4.2	12	3.9	4	1.6
D. Men aged 70 or older:										
Number men	21	—	98	—	44	—	42	—	24	—
Total sections	185	100.0	840	100.0	375	100.0	379	100.0	213	100.0
No atypical nuclei	170	91.9	13	1.5	253	67.4	15	4.0	117	54.9
Some but <60 percent atypical	15	8.1	621	74.0	118	31.5	353	93.1	93	43.7
60 percent or more atypical	—	—	206	24.5	4	1.1	11	2.9	3	1.4

[1] Sections with some epithelium present.

Source: Auerbach, O. et al. (15).

TABLE A33.—*Atypical nuclei in basal cells of epithelium of esophagus of males, by amount of smoking and age*

Cells with atypical nuclei	Never smoked regularly		Current cigarette smokers					
			<1 pack		1-2 packs		>2 packs	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
A. All ages	91	...	179	—	413	—	187	—
Total sections[1]	787	100.0	1,544	100.0	3,629	100.0	1,579	100.0
No atypical nuclei	733	93.1	89	5.8	39	1.1	39	2.5
Some but <60 percent atypical	52	6.6	1,341	86.8	2,957	81.5	1,091	69.1
60 percent or more atypical	2	0.3	114	7.4	633	17.4	449	28.4
B. Men under age 50:								
Number men	26	...	9	—	132	—	55	—
Total sections[1]	223	100.0	433	100.0	1,169	100.0	457	100.0
No atypical nuclei	190	85.2	48	11.1	21	1.8	2	0.4
Some but <60 percent atypical	33	14.8	382	88.2	1,089	93.2	382	83.6
60 percent or more atypical	...	...	3	0.7	59	5.0	73	16.0
C. Men aged 50–69:								
Number men	44	...	92	—	240	—	113	—
Total sections[1]	379	100.0	789	100.0	2,116	100.0	948	100.0
No atypical nuclei	373	98.4	30	3.8	18	0.9	35	3.7
Some but <60 percent atypical	4	1.1	694	87.9	1,607	75.9	614	64.8
60 percent or more atypical	2	0.5	65	8.3	491	23.2	299	31.5
D. Men aged 70 or older:								
Number men	21	...	38	--	41	—	19	-
Total sections[1]	185	100.0	322	100.0	344	100.0	174	100.0
No atypical nuclei	170	91.9	11	3.4	—	—	2	1.1
Some but <60 percent atypical	15	8.1	265	82.3	261	75.9	95	54.7
60 percent or more atypical	...	...	46	14.3	83	24.1	77	44.2

[1] Sections with some epithelium present.

Source: Auerbach, O. et al. (*15*).

TABLE A35.—*Summary of methods used in retrospective studies of smoking and cancer of the bladder*

Author, year, country, reference	Cases			Controls	
	Sex	Number	Method of selection	Number	Method of selection
Lilienfeld et al., 1956, U.S.A. (*171*).	M.	321	Admissions to Roswell Park Memorial Institute, 1945–55 over 45 years of age.	337	No disease patients.
	F.	116	Same as males	109	Benign bladder conditions.
				317	No disease patients.
Schwartz et al., 1961, France (*249*).	M.	214	Admissions to hospitals in Paris and a few large provincial cities since 1954.	214	Healthy individuals admitted to same hospitals because of work or traffic accident, matched by 5 year age group.
Lockwood, 1961, Denmark (*175*).	M.	282	All bladder tumors reported to Danish Cancer Register during 1942–56 and living at time of interview in Copenhagen and Fredericksburg. (Includes bladder papillomas).	282	A. From election rolls matched with cases according to sex, age, marital status, occupation, and residence.
	F.	87		87	B. Another control group obtained from sample of Danish Morbidity Survey (1952, 1953, and 1954) compared with respect to smoking histories.
Wynder, 1963, U.S.A. (*326*).	M.	200	First phase:	200	
	F.	50	Admission to several hospitals in New York City during January 1957–December 1960.	50	Admission to same hospitals (excluded cancer of respiratory system, upper alimentary tract, myocardial infarction) matched by sex and age.
			Second phase:		
	M.	100	Admission to same hospitals during 1961.	100	Same as above.
	F.	20		20	
Cobb and Ansell, 1965, U.S.A. (*57*).	M.	136	Patients admitted to VA Hospital in Seattle 1951–61.	342	120 patients with cancer of sigmoid colon, 222 patients with non-neoplastic pulmonary disease.

TABLE A35.—*Summary of methods used in retrospective studies of smoking and cancer of the bladder (cont.)*

Author, year, country, reference	Cases			Controls	
	Sex	Number	Method of selection	Number	Method of selection
Staszewski, 1966, Poland (*261*).	M.	150	Patients with histologically confirmed bladder carcinoma.	750	Undefined source age-matched.
Decley and Cohen, 1966, England (*66*).	M.	127	Patients with histologically confirmed bladder carcinoma.	127	Patients in same hospital with non-cancerous or pulmonary disease matched for age.
Yoshida et al., 1968, Japan (*330*).	M. F.	163 29	Patients with bladder cancer.	163 59	"Comparison cases."
Kida et al., 1968, Japan (*144*).	M. F.	88 26	Admissions to 15 hospitals in North Fukuoka prefecture.	88 26	Selected from patients hospitalized in same region for non-urinary ailments and age-matched
Dunham et al., 1968, U.S.A. (*85*).	M. F.	334 159	Admissions to New Orleans hospitals with histologic diagnosis of bladder carcinoma.	350 177	Admissions to same hospitals with non-neoplastic diseases and diseases unrelated to genitourinary tract.
Anthony and Thomas, 1970, England (*3*).	M.	381	Patients with papilloma and cancer of bladder at Leeds betweeen 1958-67.	275	Surgical patients without cancer previously interviewed for lung cancer study.

TABLE A35a.—*Summary of results of retrospective studies of smoking and cancer of the bladder*

Author, year, country, reference	Sex	Percent nonsmokers		Percent heavy smokers		Percent cigarettes smoked		Relative risk ratio: All smokers to nonsmokers			Comments
		Cases	Controls	Cases	Controls	Cases	Controls	All smokers	Heavy smokers	Cigarette smokers	
Lilienfeld et al., 1956, U.S.A. (*171*).	M.	15.0	29.0	...	...	61.0	44.0	2.8	...	2.7	Cigarette and other.
	F.	87.0	83.0	...	...	...	...	1.4	...	...	
Schwartz et al., 1961, France (*249*).	M.	11.0	20.0	...	...	83.0	70.0	2	...	2.2	Cigarette only.
Lockwood, 1961, Denmark (*175*).	M.	9.0	13.4	30.0	15.0	30.0	15.0	1.6	3.0	3.0	Cigarettes main mode of smoking.
	F.	56.0	66.0	4.0	4.0	...	...	1.5	1.2	...	
Wynder et al., 1963, U.S.A. (*326*).	M.	7.0	18.0	47.0	23.0	86.0	63.0	2.9	5.2	3.3	Phases A and B combined.
	F.	61.0	86.0	6.0	...	...	...	3.9	...	...	
Cobb and Ansell, 1965, U.S.A. (*57*).	M.	4.6	25.8	79.4	43.3	...	...	7.3	10.3	...	
Staszewski, 1966, Polnnd (*261*).	M.	6.7	16.0	86.7	66.7	87.1	72.2	2.7	3.1	2.9	Cigarettes only.
Deeley and Cohen, 1966, England (*66*).	M.	2.4	7.1	...	...	...	...	3.1	...	...	

TABLE A35a.—*Summary of results of retrospective studies of smoking and cancer of the bladder (cont.)*

Author, year, country, reference	Sex	Percent nonsmokers		Percent heavy smokers		Percent cigarettes smoked		Relative risk ratio: All smokers to nonsmokers			Comments
		Cases	Controls	Cases	Controls	Cases	Controls	All smokers	Heavy smokers	Cigarette smokers	
Yoshida et al., 1968, Japan (*330*).	M.	8.0	22.7	43.4	33.0	—	—	3.4	3.7	—	
	F.	62.1	86.4	—	—	—	—	—	—	—	
Kida et al., 1968, Japan (*144*).	M.	11.0	11.0	32.0	29.0	—	—	1.0	—	—	
	F.	16.0	21.0	—	—	—	—	1.4	—	—	
Dunham et al., 1968, U.S.A. (*55*).	M.	8.6	14.5	—	—	49.4	45.4	1.8	—	1.8	Cigarettes only.
	F.	62.2	61.5	—	—	32.0	28.2	1.0	—	1.1	
Anthony and Thomas, 1970, England (*3*).	F.	6.3	6.3	—	—	36.5	20.1	1.0	—	1.3	Cigarettes only. More than 15 a day.

Chapter 5

Pregnancy

Source: 1973 Report, Chapter 4, pages 97 - 149.

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Introduction

Cigarette smoking is a common habit among women of child-bearing age in the United States. In 1970, approximately one-third of American women of child-bearing age were cigarette smokers. The percentage of U.S. women who smoked throughout pregnancy is not definitely known, but is presumably lower, probably in the neighborhood of 20 to 25 percent. With a large fetal population at potential, but preventable, risk, the relationship between cigarette smoking and the outcome of pregnancy has been the focus of considerable and continuing research.

Every investigator who has examined the relationship has confirmed that the infants of women who smoke during pregnancy have a lower average birth weight than the infants of women who do not smoke during pregnancy. Much evidence indicates that cigarette smoking during pregnancy causes this reduction in infant birth weight. Several investigators have demonstrated that the fetal and neonatal mortality rate is significantly higher for the infants of smokers than for the infants of nonsmokers; other investigators have not found higher mortality for smokers' infants. Studies of the association between maternal cigarette smoking and congenital malformations have produced conflicting results.

The following is a review of work previously reported and recent studies which bear on the relationships between cigarette smoking and different outcomes of pregnancy. In addition, the chapter includes a review of the relationship between cigarette smoking and lactation.

Smoking and Birth Weight

Epidemiological Studies

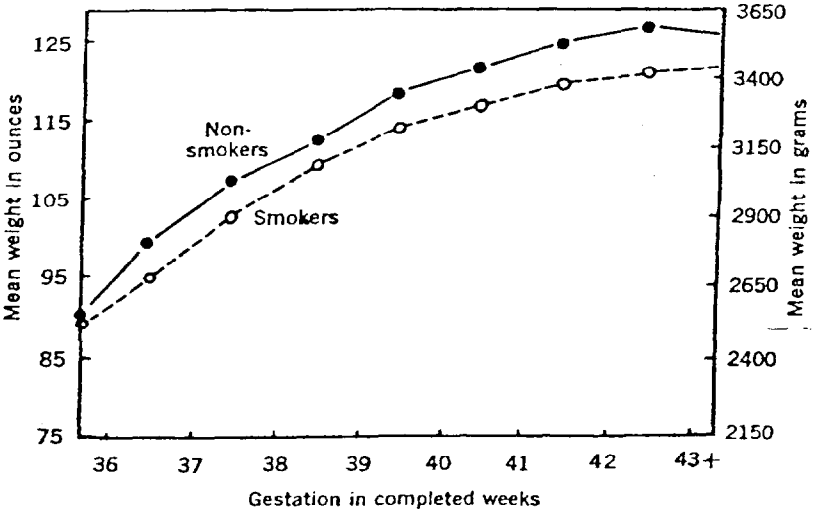
Cigarette Smoking and the Low-Birth-Weight Infant

In 1957, Simpson (*90*), using a retrospective study design, determined that among 7,499 women in San Bernardino County, Calif., the delivery of infants weighing less than 2,500 grams was nearly twice as

frequent among cigarette smokers as among nonsmokers. Subsequently, Lowe (*46*) studied 2,042 women in Birmingham, England, and demonstrated in his retrospective study that the infants of smoking mothers were delivered only slightly earlier (1.4 days on the average) than those of nonsmokers. He further noted that for gestations of 260 days and over, the infants of smokers were consistently lighter in weight during each week of gestation than those of the nonsmokers. This finding has been confirmed since, and figure 1 from the British Perinatal Mortality Study (*13*) provides illustration of this relationship.

Given the nearly constant disparity present between the birth weights of the infants of smokers and nonsmokers for gestations of 260 days and over, but absent prior to that time, and given the similar birth weights of infants of nonsmokers and of women who gave up smoking early in pregnancy and did not begin to smoke again, Lowe inferred that the influence of smoking upon birth weight might lie mainly in the later months of pregnancy. He emphasized the tentative nature of this conclusion, since the number of infants with a gestation of less than 260 days and the number of women who gave up smoking early in the pregnancy and did not begin to smoke again were both small.

Figure 1.—Mean birth weight for week of gestation according to maternal smoking habit: control week singletons.[1]



[1] This term refers to singleton births in England, Scotland, and Wales occurring during the week of March 3–9, 1958, which are included in the Perinatal Mortality Survey. These comprise 97 percent of all births notified in England and Wales or registered in Scotland during this week.

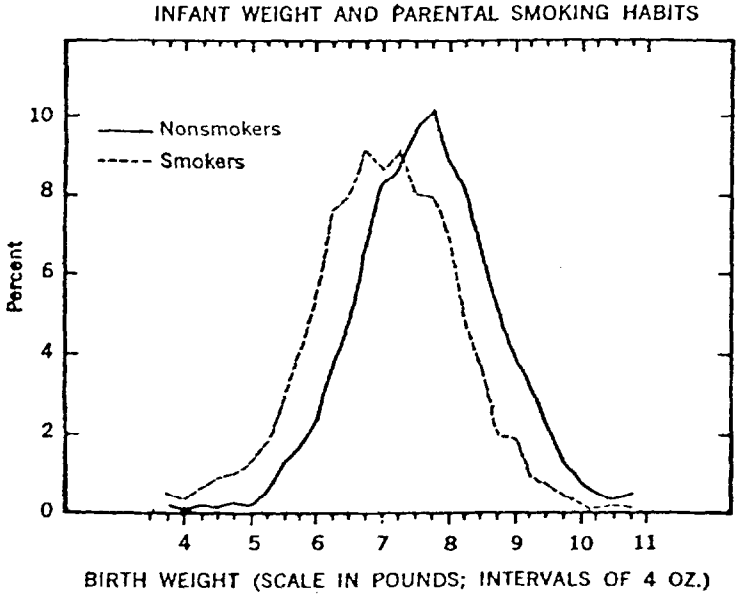
SOURCE: Butler, N. R., Alberman, E. D. (*13*).

Lowe found that the infants whose mothers smoked throughout pregnancy weighed, on the average, 170 grams less than those whose mothers did not smoke. In addition, he noted that the entire distribution of weights of infants of smokers was shifted to the left (toward lower weights) relative to that for the infants of nonsmokers. This finding, too, has been confirmed by other investigators. Figure 2 offers an illustration from MacMahon, et al. (*49*).

Given that the infants of smokers and nonsmokers differed only slightly with respect to the duration of gestation, Lowe concluded that the lower birth weight of smokers' infants must be attributed to a direct retardation of fetal growth. In other words, on the basis of his data, the infants of smokers were small-for-dates rather than truly premature.

Many investigators have subsequently confirmed this point (*12, 14, 25, 35, 65, 78, 85, 113*). Buncher (*12*), in a study of 49,897 births among U.S. naval wives, in the same population studied by Underwood, et al. (*100*), found that the infants of smokers were, on the average, delivered only 1 day earlier than those of nonsmokers. This finding accounted for only 10 percent of the discrepancy in birth weight between the two groups of infants. The remainder of the studies resulted in the detection of either similar variations in gestational length or no average difference. In a recent study, Mulcahy and Murphy (*56*),

Figure 2.—Percentage distribution by birth weight of infants of mothers who did not smoke during pregnancy and of those who smoked 1 pack of cigarettes or more per day.



SOURCE: MacMahon, et al. (49).

in a sample of 5,099 Irish mothers, concluded that although the babies born to cigarette smokers were delivered slightly earlier than those of nonsmokers, independent of age and parity, the direct effect of smoking in retarding fetal growth was more significant.

The following points, based upon the results from many different studies, can be made about the relationship between cigarette smoking during pregnancy and lower infant birth weight:

1. Women who smoke cigarettes during pregnancy have a higher proportion of low-birth-weight infants than do nonsmokers. This excess of low-birth-weight infants among cigarette smokers predominantly consists of infants who are small-for-gestational age rather than gestationally premature.
2. The entire distribution of birth weights of the infants of cigarette smokers is shifted toward lower weights compared to the birth weights of the infants of nonsmokers.
3. The birth weights of the infants of cigarette smokers are consistently lighter than those of the infants of nonsmokers when the birth weights of the two sets of infants are compared within groups of similar gestational age beyond the 36th week of gestation.

The results of the studies which have been considered so far identify a relationship between cigarette smoking and lower infant birth weight and illustrate some aspects of that relationship, but do not indicate whether the association is causal or indirect. The succeeding two sections of this chapter contain evaluations of the available evidence which bears upon the nature of the association between cigarette smoking during pregnancy and the incidence of small-for-dates infants.

Evidence for a Causal Association Between Cigarette Smoking and Small-for-Dates Infants

Evidence previously reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*) suggests that cigarette smoking is causally associated with the delivery of small-for-dates infants. The following is a summary of this evidence:

1. The results from all 30 studies in which the relationship between smoking and birth weight was examined have demonstrated a strong association between maternal cigarette smoking and delivery of low-birth-weight infants. On the average, the smoker has nearly twice the risk of delivering a low-birth-weight infant as that of a nonsmoker

(*3, 13, 17, 20, 25, 29, 35, 42, 43, 46, 47, 49, 57, 58, 59, 65, 70, 72, 73, 77, 78, 80, 83, 85, 90, 95, 99, 100, 113, 118*).

2. The strong association between cigarette smoking and the delivery of small-for-dates infants first demonstrated with results from studies of retrospective design (*3, 13, 17, 35, 46, 47, 49, 57, 58, 59, 65, 70, 72, 73, 77, 80, 85, 90, 95, 99, 100, 118*) has been repeatedly confirmed subsequently by data from studies of prospective design (*20, 25, 29, 42, 43, 78, 83, 113*).

3. A strong dose-response relationship has been established between cigarette smoking and the incidence of low-birth-weight infants (*25, 43, 46, 49, 100, 113*).

4. When a variety of known or suspected factors which also exert an influence upon birth weight have been controlled for, cigarette smoking has always been shown to be independently related to low birth weight (*1, 13, 25, 43, 46, 73, 78, 83*).

5. The association has been demonstrated in many different countries, among different races and cultures, and in different geographical settings (*13, 17, 25, 29, 36, 42, 43, 59, 73, 78, 80, 113*).

6. Previous smoking does not appear to influence birth weight if the mother gives up the habit prior to the start of her pregnancy (*25, 46, 49, 113*).

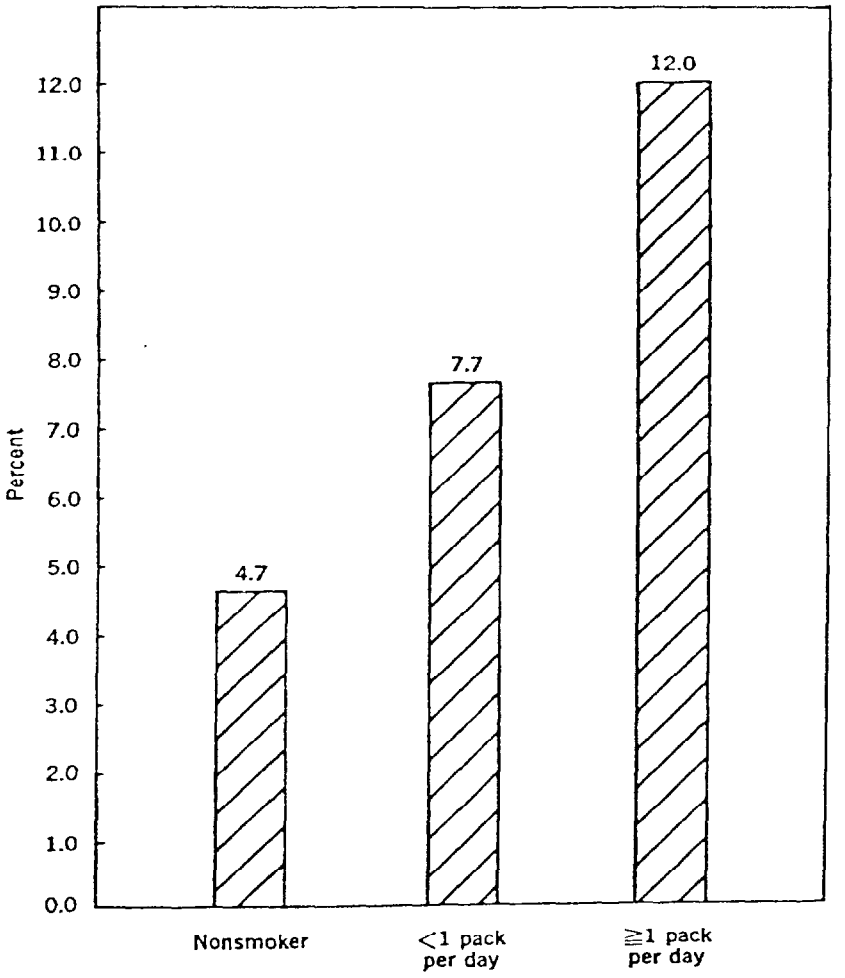
7. The infants of smokers experience an accelerated growth rate during the first 6 months after delivery, compared to infants of nonsmokers. This finding is compatible with viewing birth as the removal of the smoker's infant from a toxic influence (*83*).

8. Data from experiments in animals have documented that exposure to tobacco smoke or some of its ingredients results in the delivery of low-birth-weight off-spring (*7, 8, 9, 23, 40, 87, 117*).

Several recently published studies have provided additional supporting evidence for a causal relationship between cigarette smoking and small-for-dates infants. The Ontario Perinatal Mortality Study (*66*) was conducted among 10 teaching hospitals during 1960 and 1961. The authors of this retrospective study of 50,267 births demonstrated a significant excess of infants weighing less than 2,500 grams among cigarette smokers as compared with nonsmokers ($P<0.001$). Smoking was significantly dose-related to the percentage of pregnancies terminating in the delivery of a low-birth-weight infant (fig. 3).

Niswander and Gordon (*63*) have recently reported data from the Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke. In this prospective study of 39,200 pregnancies, which were nearly equally divided among black and white women, the authors found a significant dose-related excess of low-birth-weight infants among smokers of both groups, compared to nonsmokers of the same race.

Figure 3.—Percentage of pregnancies with infant weighing less than 2,500 grams, by cigarette smoking category.



	Nonsmoker	<1 pack per day	≧1 pack per day
Number of infants weighing <2,500 grams:	1,322	1,186	793
Total births:	28,358	15,328	6,581

(P <0.001)

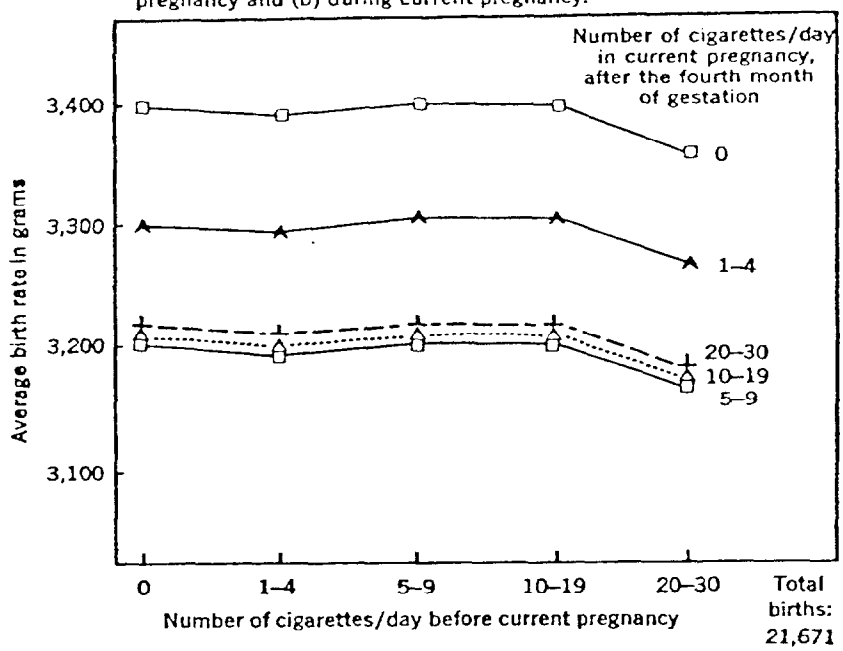
SOURCE: Ontario Department of Health (66).

Rantakallio (*76*) carried out a prospective study of 11,905 single births in Finland. Cigarette smoking mothers had significantly more infants weighing less than 2,500 grams than did nonsmokers ($P<0.001$).

Rush and Kass (*82*), in a prospective study of 1,040 pregnancies in Boston, Massachusetts; Domagala, et al. (*19*), in a retrospective study of 1,832 pregnancies in Poland; and Mukherjee and Mukherjee (*54*), in a retrospective study of 2,886 pregnancies in India, each found a significantly higher incidence of low-birth-weight infants among cigarette smokers.

Butler, et al. (*15*) have further analyzed the British Perinatal Mortality Study data. Analysis of the 16,994 questionnaires revealed that 40.8 percent of the women were cigarette smokers before pregnancy. After the fourth month, this percentage had decreased to 27.4 percent. Given the large number of women in the study, and the significant changes in smoking behavior which occurred, Butler, et al. found it possible to consider the effect of a change in smoking behavior on birth weight between the beginning of the pregnancy and the fourth month (after which smoking behavior was reportedly stable). The authors stated, "If smoking itself (rather than the type of woman who smokes) has a deleterious effect on the fetus, it would be reasonable to expect the mothers who gave up smoking during pregnancy to show differences in the birth weight and perinatal mortality of their offspring compared with those who continued to smoke." Their results are presented in figure 4. The birth weights by smoking categories were estimated by using a main effect model without mediating variables. However, the authors reported that when the mediating variables (social class, maternal age, parity, maternal height, sex of infant, gestational age, and perinatal mortality) were allowed for, the results of the analysis were very similar. The effect of cigarette smoking before pregnancy was insignificant compared to that of smoking regularly after the fourth month of gestation. The authors concluded, "The finding that a change in maternal smoking habits during pregnancy had the effect of putting the baby into a birth weight and perinatal mortality category associated with the new smoking habits points toward some kind of cause-effect relationship. * * * This finding is further strengthened by the birth weight analysis which shows that the diminution in birth weight of the offspring of smoking mothers persists and is indeed little changed when allowance has been made for a number of other social and obstetric mediating factors."

Figure 4.—Average birth weight by maternal smoking habit (a) before current pregnancy and (b) during current pregnancy.



SOURCE: Adapted from Butler, et al. (15).

Evidence for an Indirect Association Between Cigarette Smoking and Small-for-Dates Infants

Yerushalmy (*113*, *114*, *115*) has suggested that smoking is an index to a particular type of reproductive outcome and thus does not play a causal role in the production of small-for-dates infants. He has developed several lines of support for this hypothesis, from an analysis of data from the prospective investigation of 13,083 mothers in the Oakland Child Health and Development Study. He has emphasized that ineffective randomization and the phenomenon of self-selection complicate the development of appropriate inferences with regard to causality. Such difficulties do not prevent the identification of causal associations, but they demand careful and critical analysis of the data. Yerushalmy has questioned the causal nature of the relationship between cigarette smoking and small-for-dates infants because of: (a) The relationship between the smoking habit of the father and low birth weight of the infant, (b) behavioral differences between smokers and nonsmokers, and (c) comparison of the birth weights

of a woman's infants born during the periods when she smoked cigarettes and when she did not.

Yerushalmy (*114*) has stated that the smoking habit of the father could not reasonably be related to the birth weight of the infant. From preliminary data derived from the study, however, he determined that there was an increased incidence of low-birth-weight infants when the fathers smoked and, moreover, there was an apparent dose-response relationship as found for maternal smoking. However, he noted that only when both the husband and the wife smoked was the incidence of low-birth-weight babies increased. He felt that these findings supported the conclusion that smoking was a marker of types of individuals and not a causal factor for low birth weight. Other investigators have since examined this relationship (*49*, *100*), but none has confirmed an independent association for paternal smoking. The association between paternal smoking and birth weight appears to be an indirect one. Paternal and maternal smoking behavior are highly correlated and maternal smoking is strongly related to infant birth weight. Underwood, et al. (*100*) studied 48,505 women, their husbands' smoking behavior, and the relation with birth weight (table 1). If the mother was a nonsmoker, then the father's smoking had no influence on the birth weight of the infant.

TABLE 1.—*Infant birth weight by maternal and paternal smoking habits*

Cigarettes per day	Mothers			Fathers (nonsmoking mothers)		
	Number	Birthweight (grams)		Number	Birthweight (grams)	
		Mean	Difference[1]		Mean	Difference[1]
None	24,865	3,395	0	9,547	3,396	0
1 to 10	7,609	3,286	109	3,493	3,389	7
11 to 30	14,450	3,196	199	10,403	3,391	5
>30	1,570	3,182	213	1,330	3,393	3

[1] Nonsmoker minus smoker.

Source: Underwood, et al. (*100*).

Yerushalmy (*115*) pointed out that other investigators had found marked differences between smokers and nonsmokers. In his own study, he found that nonsmokers used contraceptives significantly more frequently than did smokers. Moreover, a significantly higher proportion of smokers drank coffee, beer, and whiskey. However, he did not adjust for these variables in his analysis of the association between cigarette smoking and lower infant birth weight. Other investigators have also found differences between smokers and nonsmokers. For example, Frazier, et al. (*25*) found significant differences in the distribution of parity, work history, education, and psycho-

somatic complaint score between smokers and nonsmokers. However, when smokers were compared with nonsmokers of the same parity, education, work history, and psychosomatic complaint score, cigarette smokers still had a significantly higher proportion of small infants than did nonsmokers. As previously mentioned, whenever other factors known or suspected to influence birth weight have been controlled, cigarette smoking has always been demonstrated to have an independent and significant effect.

Ounsted (*69*) offered evidence that the best predictor of the birth weight of a mother's future offspring was the birth weight of her previous children. Herriott, et al. (*35*) found prematurity rates for previous pregnancies among smokers to be markedly higher than among nonsmokers, independent of parity, height, and social class. Evidently a woman whose previous infants have been small tends to continue to have relatively smaller than average infants in subsequent pregnancies. The question is, will those infants be even smaller than expected if she smokes?

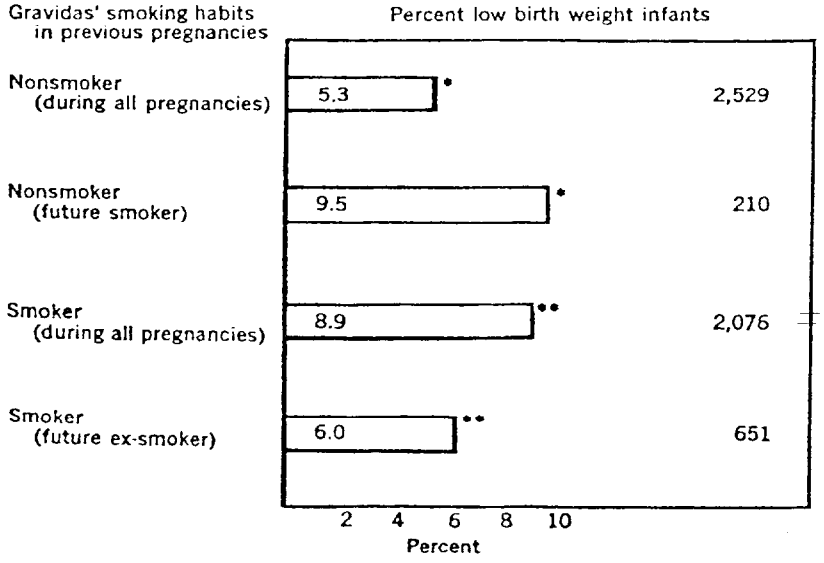
Goldstein, et al. (*28*), in a comprehensive review, proposed a research design in which a woman would serve as her own control to compare outcomes of pregnancies during which she smoked with those during which she did not with consideration of the effect of parity on the outcome. Yerushalmy (*112*) has recently tested this type of research design, using data from his Oakland Growth Study. With information on the age at which a woman began to smoke cigarettes, her smoking status during the pregnancy actually studied, her prior reproductive experience, and the outcome of her present pregnancy, the author compared the outcomes of pregnancy during periods of smoking and nonsmoking using the woman as her own control. As the author noted, "If smoking *causes* the increase in low-birth-weight infants, then the incidence of low birth weight for infants born to smoking mothers during the period before they acquired the smoking habit, should be relatively low. If, on the other hand, the high incidence of low birth weight is due to the *smoker*, then it should be high for infants of future smokers also when they were born before their mothers started to smoke."

Yerushalmy then proceeded to compare the reproductive experiences of four groups of women: (a) Those who smoked in none of their pregnancies, (b) those who smoked in all of their pregnancies, (c) those who were smoking now but previously had not smoked during some pregnancies (future smokers), and (d) those who were ex-smokers now but had previously smoked during some pregnancies. These outcomes are shown in figure 5. The incidence of low-birth-weight infants in the pregnancies of the future smokers, before they started to smoke, was similar to that for women who smoked in every pregnancy, which was significantly higher than that of infants from

mothers who had never smoked. He also noted that ex-smokers, during the period before they quit, gave birth to relatively few low-birth-weight infants; the incidence was significantly lower than for mothers who smoked during all of their pregnancies. He concluded that the findings cannot be easily reconciled with a cause-effect basis for smoking and birth weight. He said, "Rather the evidence appears to support the hypothesis that the higher incidence of low-birth-weight infants is due to the *smoker*, not the *smoking*."

There are several considerations which limit the interpretations which can be drawn from this study. The information on smoking behavior of the women during past pregnancies was apparently derived from the woman's age when she began to smoke, her smoking behavior early in the study pregnancy, and the age at which she had her prior pregnancies. Thus, if the woman reported that she began smoking at a certain age, and that she was still smoking at the time of the study, it was apparently inferred that she had smoked during all of her pregnancies. Since no questions were specifically asked about actual smoking behavior during each previous pregnancy, it is possible that the woman indeed had not smoked during every pregnancy or that the amount or way she smoked had differed from current smoking

Figure 5.—Percent of low birth weight white infants by smoking status of their mothers.



*Difference is statistically significant (P <0.01).
**Difference is statistically significant (P <0.02).

SOURCE: Adapted from Yerushalmy, J. (112).

habits. This would be important to know given the strong dose-response relationship which has been established between cigarette smoking and low birth weight, and would tend to make the reproductive outcomes for ex-smokers similar to those of nonsmokers, and different from those of women who smoked in all pregnancies.

For ex-smokers, the age at which smoking began was not elicited. Hence, some of the infants of ex-smokers may have been born before their mothers acquired the smoking habit. This would also tend to make the reproductive experiences of ex-smokers more like those of nonsmokers and different from those of women who smoked in all pregnancies.

No direct adjustment for age, parity, and other variables was reported, although Yerushalmy stated that the study population was limited to the births that occurred to women at age 25 years or less. He noted that, "In order to adjust for parity, the same comparisons were performed for firstborn infants only. The numbers were reduced considerably, but the same tendencies as found above were noted." However, no data were presented. Primiparous births and births in teenagers are strongly associated with the delivery of low-birth-weight infants. If the pregnancies which occurred among future smokers included a predominance of very young women and primiparous births, the reproductive experiences of future smokers would tend to be similar to those of women who smoked during all pregnancies, and different from those of nonsmokers. In the absence of more precise information on actual smoking behavior during pregnancy and more rigorous adjustment for maternal age, this study does not provide a critical test of the hypothesis that it is the smoking during pregnancy which is responsible for the high proportion of small-for-dates infants born to women who smoke.

Experimental Studies

Studies in Animals

Tobacco Smoke

Several investigators have demonstrated that exposure of pregnant rats or rabbits to tobacco smoke leads to a reduction of birth weight in the offspring, as compared to controls (*23, 87, 117*). Younoszai, et al. (*117*) reported data from studies in rats which indicated that some agent present in cigarette smoke other than nicotine was responsible for the reduction in birth weight observed. The authors suggested that carbon monoxide might also not be responsible for the retardation of

fetal growth; however, the evidence presented was inadequate to support a firm conclusion.

Haworth and Ford (*33*) recently extended the experiments of Younoszai. A group of pregnant rats was exposed to cigarette tobacco smoke for 6 to 8 minutes, five times a day, from days 3 to 20 of gestation. These rats were compared with another group whose food intake was restricted to the amount actually consumed by the tobacco-exposed rats, and both were compared to a well-fed control group. The animals in both experiments were killed on the 21st day of gestation, and weights of the entire body, the liver, and the kidney of each fetus were recorded. The total average fetal weight of the group exposed to tobacco smoke was significantly lower than that of both the food-restricted and control groups. The fetal weights of the latter two groups were quite similar. Protein and DNA analyses were performed separately on the entire forebrains and hindbrains of the fetuses and on the entire carcass. Both DNA and protein were significantly and proportionately reduced in the carcass and hindbrains of the animals exposed to tobacco smoke. This implies that cell number was reduced and cell size was normal, and suggests that the exposure to tobacco smoke either inhibited cellular proliferation or accelerated cellular destruction.

Nicotine

Several workers have demonstrated that chronic injections of large doses of nicotine into pregnant rats resulted in a reduction of birth weight of the offspring (*7*, *8*, *9*, *23*, *40*). Other investigators have determined that tritium-labelled nicotine injected into pregnant rabbits and C^{14}-labelled nicotine injected into pregnant mice crossed the placenta to the developing embryo and fetus (*89*, *98*). Kirschbaum, et al. (*41*) found no significant acute effects of small doses of nicotine, injected intravenously into near-term sheep, on blood gas composition, pH, blood pressure, or heart rate in either the ewes or their fetuses. The authors concluded that the influence of maternal smoking upon the fetus must result from chronic effects or through the effects of other variables which they did not study.

Recently, Suzuki, et al. (*94*) evaluated the short-term effects of injected nicotine on the cardiovascular performance, acid-base status, and oxygenation of pregnant female Rhesus monkeys and their infants during the second half of gestation using the mothers as their own controls. Nicotine was administered either as a single intravenous dose of 0.5 to 1.0 mg. or as a continuous infusion of 100 μg./kg. over

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a 20-minute period. The injection of nicotine in the larger, single dose into the mother produced a rise in maternal blood pressure and a fall in maternal heart rate, and an immediate fall in both fetal blood pressure and fetal heart rate followed by persistent hypotension and tachycardia in the fetus. Subsequent to the injection of 1.0 mg./kg. of nicotine into pregnant monkeys, in a single dose, significant changes in the arterial blood of the older fetuses included a fall in pH, a rise in base deficit, and a fall in oxygen tension. Carbon dioxide tension remained unchanged. Nicotine injected directly into the fetus prompted an immediate rise in fetal blood pressure and a fall in fetal heart rate. These responses were similar to those previously seen in the mothers following a direct injection of nicotine. The changes were more prominent in older rather than in younger fetuses. The authors summarized their findings by stating that: (a) fetuses in different gestational stages are differentially responsive to a given dose of nicotine, probably because of the different stages of development of the autonomic nervous system; (b) diminished intervillous space perfusion resulting from vasoconstriction in the uterine circulation appears to be mainly responsible for the fetal asphyxia following the injection into the mother, because fetal hypotension and bradycardia were not preceded by the transient hypertension seen following the direct administration of nicotine to the fetus; (c) the differences between the results obtained by Kirschbaum and by Suzuki, et al. may reflect either the considerable dosage differences or species differences; and (d) the doses which the authors employed were much larger than those which a human mother would absorb from usual cigarette smoking, but that differences in tolerance to nicotine between the Rhesus monkey and humans would imply that the dosages were, in fact, comparable and that, "Hence, it can be envisaged that the concentration of nicotine which could be reached in the organism of a smoking mother would reduce oxygen availability to the fetus."

Carbon Monoxide

Longo (*45*) has reviewed the work of several investigators which has demonstrated the transplacental passage of carbon monoxide from mother to fetus in animals. A recent study which related CO to birth weight was published by Astrup (*2*). He found that continuous exposure throughout gestation of pregnant rabbits to different levels of ambient carbon monoxide resulted in a statistically significant dose-related reduction in birth weight (table 2). The actual significance level was not reported.

TABLE 2.—*Effect of carbon monoxide exposure of pregnant rabbits on birth weight*

	Group 1, 0 percent COHb	Group 2, 8 to 10 percent COHb	Group 3, 16 to 18 percent COHb
Number of pregnant rabbits	17	14	17
Total number of babies	116	81	123
Average weight of babies in grams	53.7	51.0	44.7

SOURCE: Astrup, P. (*6*).

Polycyclic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) such as benzo(a)pyrene (BAP) are constituents of cigarette smoke which have been implicated in the generation of cancers in many animal species (*111*). No studies presently available relate benzo(a)pyrene to a reduction in birth weight of exposed offspring. Evidence suggests, however, that BAP does reach and cross the placenta. Aryl hydrocarbon hydroxylase (AHH) is a part of the cytochrome P–450– containing microsomal enzyme system, present in many tissues of different species. This enzyme system is induced to hydroxylate polycyclic aromatic hydrocarbons after exposure of cells to PAH. Several investigators have utilized the inducibility of the enzyme system to demonstrate indirectly that benzo(a)pyrene and other polycyclic hydrocarbons reach the placenta and fetus.

Welch, et al. (*108*) extended this work by administering the polycyclic hydrocarbon, 3-methylcholanthrene (3-MC), to rats during late gestation. The metabolism of benzo(a)pyrene was studied in vivo (using tritium-labelled benzo(a)pyrene) and in vitro. AHH activity was increased in fetal livers to adult levels by pretreatment with 3-MC Since a relatively high dose of polycyclic hydrocarbon was required to stimulate enzyme activity in the fetus, compared to the dose which stimulated placental enzyme activity, the authors suggested that the placenta may protect the fetus from exposure to polycyclic hydrocarbons. However, immaturity of the fetal enzyme system might also account for its apparent relative insensitivity to polycyclic hydrocarbons. Therefore, an exposure of the fetus to levels of polycyclic hydrocarbon similar to those experienced by the mother cannot be ruled out by the available data.

Schlede and Merker (*86*) have studied the effect of benzo(a)pyrene administration on aryl hydrocarbon hydroxylase activity in the maternal liver, placenta, and fetus of the rat during the latter half of gestation. The pregnant animals were treated with large oral doses of benzo(a)pyrene 24 hours prior to sacrifice. Control rats had no detectable levels of aryl hydrocarbon hydroxylase in their placentas. Treatment with benzo(a)pyrene resulted in barely detectable placental levels on gestation day 13, but steadily rising values until day 15, and then constant levels thereafter. No activity was detected in the fetuses of untreated controls. In the treated animals, the fetal enzyme activity rose steadily from the 13th to the 18th day of gestation. The authors concluded that the stimulatory effect of benzo(a)pyrene treatment on aryl hydrocarbon hydroxylase activity in the fetus demonstrates that benzo(a)pyrene readily crosses the rat placenta.

Studies in Humans

Carbon Monoxide

Smokers and their newborn infants have significantly elevated levels of carbon monoxide as compared with nonsmokers and their infants (*31*, *34*, *88*, *116*). Recently, Baribaud, et al. (*5*) studied 50 nonsmokers and 27 cigarette smokers and their newborns. All smokers inhaled. The authors found that the mean level of CO content in the blood of nonsmokers was 0.211 volumes percent compared with 0.672 volumes percent in the blood of smokers. The values for blood samples from the umbilical cords of their newborns were 0.352 and 0.949 volumes percent, respectively. Moreover, a definite dose relationship was found between CO levels and number of cigarettes smoked.

Younoszai, et al. (*116*) found, in addition to elevated carboxyhemoglobin levels among the infants of smoking mothers, significant elevation of mean capillary hemotocrits and significant reduction of standard bicarbonate levels, as compared to the infants of nonsmoking mothers. Since no evidence for nicotine effects upon blood glucose, serum FFA levels, or urinary catecholamines, or for hypoxia was present, they concluded that the higher hematocrit levels in the infants of smoking mothers may have represented a compensatory response to the decreased oxygen-carrying capacity of the blood due to the presence of carboxyhemoglobin.

Longo (*45*) pointed out that a level of 9 percent carboxyhemoglobin in the fetus is the equivalent of a 41 percent decrease in fetal blood flow or fetal hemoglobin concentration. In reviewing the studies of CO levels in human mothers and their newborns, he made the follow-

ing comments: "These samples were obtained at the time of vaginal delivery or Cesarean section and may not accurately reflect the normal values of $(COHb)_F$ for several reasons. The number of cigarettes smoked by the mothers during labor may be less than their normal consumption and was not specified in these studies. The blood samples were collected at varying time periods following the cessation of smoking. In addition, many of the samples were probably taken early in the day before COHb levels had built up to the levels reached after prolonged periods of smoking. Thus actual levels of $(COHb)_M$ and $(COHb)_F$ may be higher than the reported values."

Polycyclic Hydrocarbons

The results of several studies concur that cigarette smoking is strongly associated with the induction of aryl hydrocarbon hydroxylase in the human placenta (*18*, *38*, *61*, *99*, *109*). This finding implies that benzo(a)pyrene or other polycyclic hydrocarbons reach the placenta. To date, evidence to support the passage of polycyclic hydrocarbons through the placenta to the human fetus has not been published.

Vitamin B_{12} and Cyanide Detoxification

McGarry and Andrews (*48*) determined serum vitamin B_{12} levels in 826 women at their first prenatal clinic visit. They found that the serum levels for smokers were significantly lower than for nonsmokers. After adjustment for gestational age, parity, social class, hemoglobin level, hypertension, and maternal weight, smokers still had significantly lower levels of B_{12}. They also found a direct, statistically significant dose-response relationship between cigarettes smoked and serum vitamin B_{12} level. They again confirmed the relationship between smoking and low birth weight. The authors suggested that the lowered vitamin B_{12} levels reflect a disorder of cyanide detoxification. Cyanide is a demonstrable ingredient in cigarette smoke (*39*, *60*, *62*, *64*, *68*, *74*, *91*).

Vitamin C

Venulet (*105*, *106*, *107*) has demonstrated that the vitamin C level is significantly lower in the serum of women who smoke cigarettes during pregnancy, compared to values for their nonsmoking counterparts.

Possible Mechanisms

The following mechanisms have been proposed for the production of low birth weight and other unfavorable outcomes of pregnancy following exposure to cigarette smoke:

1. A direct toxic influence of constituents of cigarette smoke upon the fetus (*2*, *45*, *50*, *51*, *117*).
2. Decreased placental perfusion (*94*).
3. Decreased maternal appetite and diminished maternal weight gain with secondary effects upon the fetus (*6*, *33*, *36*, *65*, *75*, *99*-*117*).
4. A direct effect upon the placenta (*36*, *57*, *65*, *110*).
5. An oxytocic effect on uterine activity (*44*).
6. A disturbance of vitamin B_{12} metabolism (*48*).
7. A disturbance of vitamin C metabolism (*105*, *106*, *107*).

Of the potential mechanisms, available evidence suggests that neither decreased maternal appetite and decreased maternal weight gain nor a direct effect upon the placenta are responsible for a significant reduction in birth weight. Existing evidence does not permit firm conclusions concerning the relative significance of the remaining mechanisms.

Timing of the Influence of Cigarette Smoking on Birth Weight

Several investigators have published results which bear on the time period during which exposure to cigarette smoke most affects fetal growth. Lowe (*46*) and Zabriskie (*118*) have offered evidence which suggests that cigarette smoking influences fetal growth most during the second half of pregnancy. Butler, et al. (*15*) found that the birth weights of infants of women who did not smoke after the fourth month of pregnancy were essentially the same as those of the infants of nonsmokers. This implies that the influence is most probably exerted after the fourth month of pregnancy. Herriott, et al. (*35*), however, found that women in lower socioeconomic classes who gave up smoking early in pregnancy tended to have intermediate weight babies as compared with nonsmokers and persistent smokers, but his numbers of women were small and the results were not statistically significant. Underwood, et al. (*100*) found that cigarette smoking in any single trimester was associated with a lower birth weight of the infant, although the difference between the birth weights of infants of women who smoked only during a single trimester and infants of nonsmokers was not statistically significant because of small numbers. Several investigators have detected a nearly constant difference between the birth weights of the infants of smokers and nonsmokers, delivered during the last month of pregnancy, following gestations of comparable length [fig. 1, (*11*)]. Although this observation is

compatible with the suggestion that the influence of cigarette smoking upon the fetus occurs prior to the last month of pregnancy, it is based upon data derived from cross-sectional rather than longitudinal studies. The results of many human epidemiological studies suggest that maternal smoking prior to pregnancy does not influence fetal weight gain (*15*, *25*, *46*, *49*, *113*).

Site of Action at the Tissue and Cellular Level

The use of labelled nicotine (*98*) and the preparations of autoradiograms have permitted the localization of nicotine within the tissues of the fetus and mother. Tjalve, et al. (*98*) found high levels of nicotine in the respiratory tract, adrenal, kidney, and intestine of 16- to 18-day mice fetuses. The use of other labelled constituents during various parts of gestation might further the understanding of how certain ingredients in cigarette smoke produce an impact upon birth weight. Haworth and Ford (*33*) have reported data which suggest that the reduction of birth weight of rat fetuses caused by the action of the ingredient(s) of tobacco smoke results from a reduction in cell number, but not in cell size.

Significance of the Association

Among all women in the United States, cigarette smokers are nearly twice as likely to deliver low-birth-weight infants as are nonsmokers. Assuming that 20 percent of pregnant women in the United States smoked cigarettes through the entire pregnancy (extrapolated from data on changes in smoking behavior during pregnancy collected for the British Perinatal Mortality Study), taking into account the apparently different risks of delivering a small-for-dates infant for Caucasian and non-Caucasian women who smoke during pregnancy, and considering the number of infants with a birth weight less than 2,500 grams born to Caucasian and non-Caucasian women, an excess of nearly 43,000 occurred in the 286,000 low-birth-weight infants among the 3,500,000 infants born in the United States in 1968, because of the increased risk among women who smoke of having small-for-dates infants.

Since neonatal mortality is higher for low-birth-weigth infants, with gestational age held constant, the excess of small-for-dates infants among smoking mothers would imply a significant excess mortality risk as well.

A causal association between cigarette smoking and fetal growth retardation is supported by the following evidence:

1. The results of all 42 studies in which the relationship between smoking and birth weight was examined have demonstrated a strong association between cigarette smoking and delivery of small-for-dates infants. On the average, the smoker has nearly twice the risk of delivering a low-birth-weight infant as that of a nonsmoker.
2. This association has been confirmed by both retrospective and prospective study designs.
3. A strong dose-response relationship has been established between cigarette smoking and the incidence of low-birth-weight infants. Available evidence suggests that the effect of smoking upon fetal growth reflects the number of cigarettes smoked daily during a pregnancy, and not the cumulative effect of cigarette smoking which occurred before the pregnancy began.
4. When a variety of known or suspected factors which also exert an influence upon birth weight have been controlled for, cigarette smoking has consistently been shown to be independently related to low birth weight.
5. The association has been found in many different countries, among different populations, and in a variety of geographical settings.
6. New evidence suggests that if a woman gives up smoking by the fourth month of pregnancy, her risk of delivering a low-birth-weight infant is similar to that of a nonsmoker.
7. The infants of smokers experience a transient acceleration of growth rate during the first 6 months after delivery, compared to infants of nonsmokers. This finding is compatible with viewing birth as the removal of the smoker's infant from a toxic influence.
8. The results of experiments in animals have shown that exposure to tobacco smoke or some of its ingredients results in the delivery of low-birth-weight offspring. New evidence demonstrates that chronic exposure of rabbits to carbon monoxide during gestation results in a dose-related reduction in the birth weight of their offspring.
9. Data from studies in humans have demonstrated that smokers' fetuses are exposed directly to agents within tobacco smoke, such as carbon monoxide, at levels comparable to those which have been shown to produce low-birth-weight offspring in animals.

Cigarette Smoking and Fetal and Infant Mortality

Introduction

Several previous studies of the relationship between cigarette smoking and higher fetal and infant mortality among the infants of smokers have been reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*). In many of these studies, the authors combined two or more categories of fetal and infant mortality. Different mortality outcomes, such as spontaneous abortion, stillbirth, and neonatal death, are influenced by different sets of factors. Among other factors, the frequency of abortion is influenced by congenital infections, hormonal deficiencies, and cervical incompetency. In addition to other factors, the frequency of stillbirth is influenced by premature separation of the placenta, uterine inertia, and dystocia. Along with other factors, the frequency of neonatal death is influenced by gestational maturity, birth injuries, and delivery room and nursery care. Separate analysis of the relationship of cigarette smoking to each different mortality outcome, with control of the unique set of factors which influences it, may facilitate understanding of the relationship.

Spontaneous Abortion

Previous epidemiological and experimental studies of the relationship between spontaneous abortion and cigarette smoking reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*) form the basis of the following statements:

The results of several studies, both retrospective and prospective, have demonstrated a statistically significant association between maternal cigarette smoking and spontaneous abortion (*43*, *65*, *70*, *99*, *118*). Data from some of these studies have documented a strong dose-response relationship between the number of cigarettes smoked and the incidence of spontaneous abortions (*70*, *99*, *118*). In general, variables other than cigarette smoking (e.g., maternal age, parity, health, desire for the pregnancy, and use of medication), which may influence the incidence of spontaneous abortions, have not been controlled. The results of the one study, in which adjustment for the woman's desire for the pregnancy was performed, indicated that after such adjustment cigarette smoking during the pregnancy retained an association with spontaneous abortion of borderline significance (*43*). The time period during which cigarette smoking might exert an influence on the incidence of spontaneous abortions has not been determined. Abor-

tions have been produced in animals only with large doses of nicotine (*23*, *96*, *104*); the relevance of these studies for humans is uncertain.

Spontaneous Abortion Summary

Although several investigators have found a significantly higher, dose-related incidence of spontaneous abortion among cigarette smokers as compared to nonsmokers, the lack of control of significant variables other than cigarette smoking does not permit a firm conclusion to be drawn about the nature of the relationship.

Stillbirth

Epidemiological studies of the association between cigarette smoking and stillbirth previously reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*) form the basis for the following statements:

In one group of retrospective and prospective studies, a higher stillbirth rate was found for the infants of smokers as compared to those of nonsmokers (*14*, *25*, *43*). In another group of retrospective and prospective studies, no significant difference was detected in the stillbirth rate among the infants of smokers and nonsmokers (*16*, *20*, *85*, *99*, *100*). Differences in study size, numbers of cigarettes smoked, or the presence or absence of control of variables, such as age and parity, which may influence stillbirth rates, were probably not sufficient to explain the differences in results obtained.

Several recent epidemiological studies have added to our understanding of the relationship between cigarette smoking and stillbirth. Niswander and Gordon (*63*) have reported data from 39,215 pregnancies followed prospectively and collected between 1959 and 1966 at 12 university hospitals in the United States. A random sample of women who presented to hospital prenatal clinics were enrolled in the study. The authors reported no increase in stillbirths among white smokers as compared with white nonsmokers. A higher incidence of stillbirths was found among black women who smoked than among nonsmoking black women, and a dose-response relationship with cigarettes smoked was suggested, although the findings did not attain statistical significance. The results were not adjusted for other variables. Rush and Kass (*82*) found, in a prospective study of 3,296 pregnancies at Boston City Hospital, a nonsignificant increase in

stillbirths among white women who smoked, but a statistically significant increase in stillbirths among black women who smoked ($P<0.02$). These findings are consistent with those previously outlined by Frazier, et al. (*25*) and Underwood, et al. (*99*).

Rumeau-Roquette (*81*), in a prospective study of 4,824 pregnancies in Paris, demonstrated that the risk of stillbirth was significantly higher for cigarette smokers than for nonsmokers ($P<0.001$). The authors also presented evidence that a woman with either a previous stillbirth or at least one prior infant weighing less than 2,500 grams at birth was significantly more likely to have a future stillborn infant than a woman without such an obstetrical history. After previous obstetrical history was controlled, smokers still retained a statistically significant increased risk of subsequent stillbirth as compared to nonsmokers ($P<0.01$). Of further interest was the finding that among women who previously had delivered only living infants, weighing over 2,500 grams, cigarette smoking had no influence on the stillbirth rate.

Previous experimental studies were reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*). The authors demonstrated that exposure of pregnant rabbits to tobacco smoke and pregnant rats tc large doses of injected nicotine resulted in a significant increase in stillbirths (*7*, *8*, *23*, *87*).

Stillbirth Summary

1. The results of recent studies suggest that cigarette smoking is most strongly associated with a higher stillbirth rate among women who possess less favorable socioeconomic surroundings or an unfavorable previous obstetrical history. In the United States, black women have higher stillbirth rates than white women. The finding that cigarette smoking is associated with an even greater difference between the stillbirth rates of the two groups merits special attention. These findings may provide at least a partial explanation for the lack of a significant difference in stillbirth rates between smokers and nonsmokers, which some investigators have found.
2. The results of experiments in animals demonstrate that exposure to tobacco smoke and some of its ingredients, such as nicotine, can result in a significant increase in stillbirth rate.

Late Fetal and Neonatal Deaths

Considerable variation has occurred in the definition of the study population among the studies in which the relationship of cigarette smoking to fetal mortality (other than abortion) and early infant mortality was examined. The most commonly identified study populations have been perinatal deaths, neonatal deaths, and late fetal plus neonatal deaths. Perinatal deaths are a combination of late fetal deaths (i.e., stillborn infants) and deaths occurring within the first week of life. Neonatal deaths include all deaths of liveborn infants within the first 28 days of life.

Epidemiological Studies

Most of the earlier epidemiological studies of the association between cigarette smoking and late fetal plus neonatal mortality were reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*). A review of previously unreported studies (*67*, *76*), as well as reexamination of previously cited studies, forms the basis of the following statements:

The results of several prospective and retrospective studies indicate a statistically significant higher late fetal and/or neonatal mortality for the infants of smokers compared to those of nonsmokers (*14*, *17*, *25*, *43*). The results of other prospective and retrospective studies identified no significant difference in the mortality rates between the infants of smokers and nonsmokers (*20*, *65*, *72*, *85*, *100*, *115*).

If mortality rates were compared for those infants of smokers and nonsmokers weighing less than 2,500 grams, the infants of nonsmokers apparently had a considerably higher risk than did those of smokers.

The results of recent studies, coupled with a critical review of the design and analysis of previous studies, and a reexamination of existing data, may provide at least a partial explanation of discrepancies between the results of previous studies.

Comparisons of the Mortality Risks of Low-Birth-Weight Infants Born to Smokers and Nonsmokers

The perinatal mortality risk for infants weighing less than 2,500 grams appears to be lower for those infants born to women who smoke during pregnancy than for those born to nonsmokers (table

3). However, available evidence shows that cigarette smokers' infants tend to be small-for-gestational age rather than gestationally premature. Hence, within a given birth weight group, the infants of smokers are, on the average, gestationally more mature than those of nonsmokers. Data collected by the National Center for Health Statistics (*103*) demonstrate that within a given birth weight group, the more gestationally mature an infant, the lower is its mortality risk (fig. 6). Thus, the difference in perinatal mortality risks experienced by the infants of cigarette smokers and nonsmokers, within comparable birth weight classes, reflects the facts that the two sets of infants are not of the same average gestational age, and that gestational age is a major factor influencing late fetal and neonatal mortality. An accurate estimate of comparative mortality risks for the infants of cigarette smokers and nonsmokers requires adjustment for gestational age.

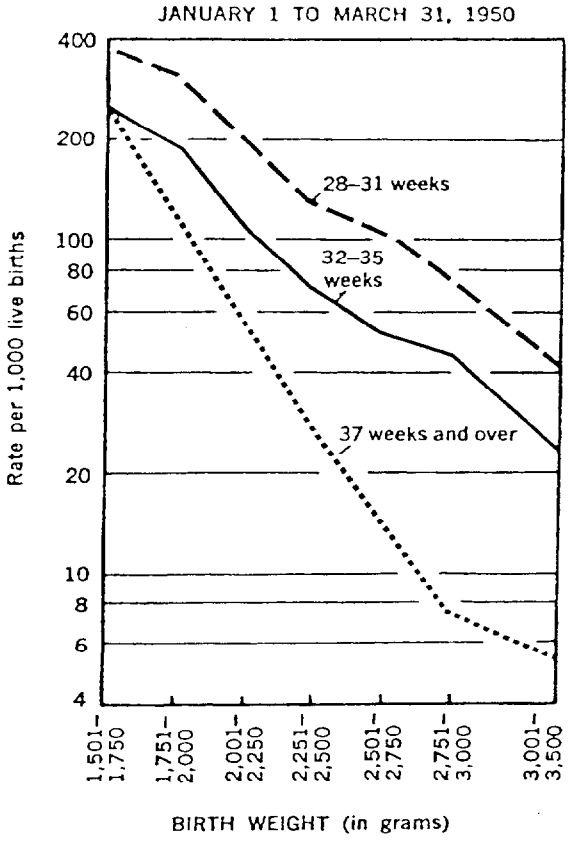
For infants of comparable gestational age, lower birth weight is associated with higher mortality (fig. 6). Since infants of cigarette smokers have, on the average, lower birth weights than the infants of nonsmokers, within groups of comparable gestational age, cigarette smokers' infants should experience higher mortality rates than nonsmokers' infants of similar gestational ages. In a recent review, Meyer and Comstock (*51*) provided a more extensive discussion of these points.

TABLE 3.—*Comparison of the perinatal mortality for infants weighing less than 2,500 grams, of smokers and nonsmokers*

Author, reference	Perinatal mortality rate (deaths per 1,000 live births)	
	Smokers	Nonsmokers
Underwood, et al. (*100*)	187	269
Ontario Department of Health (*67*)	232	300
Kullander and Källen (*43*)	129	139
Rantakallio (*76*)	288	344
Yerushalmy [1] (*112*):		
Black women	114	202
White women	114	218
Butler and Alberman (*14*)	269	284

[1] Reported neonatal mortality rates only.

Figure 6.—Neonatal mortality rates among single white births in hospitals (by detailed birth weight and specified gestation groups: United States).

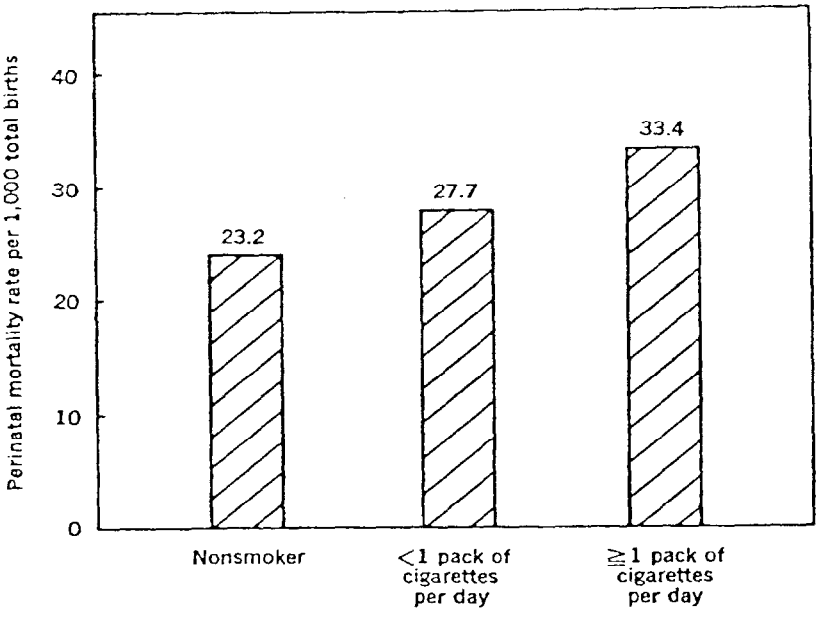


SOURCE: U.S. Public Health Service, National Center for Health Statistics *(103)*.

Recent Studies

The Ontario Perinatal Mortality Study (*66*, *67*) was conducted among 10 teaching hospitals during 1960 and 1961. In this retrospective study of 51,490 pregnancies, a statistically significant increase in the perinatal mortality rate was demonstrated for smokers' infants as compared with those of nonsmokers; the infants of smokers experienced an overall relative risk of 1.27 ($P<0.001$). Moreover, the investigators found a statistically significant dose-response relationship between the amount of cigarettes smoked and the perinatal mortality rate ($P<0.001$) (fig. 7).

Figure 7.—Perinatal mortality rate per 1,000 total births by cigarette smoking category.



	Nonsmoker	<1 pack of cigarettes per day	≥1 pack of cigarettes per day
Number of perinatal deaths:	659	425	220
Total births:	28,358	15,328	6,581

($P < 0.001$)

SOURCE: Ontario Department of Health (66).

Recently Butler, et al. (*15*) further analyzed the British Perinatal Mortality Study. They found a highly significant association between maternal smoking after the fourth month of pregnancy and both late fetal and neonatal deaths. Infants of smokers had an increase in the late fetal mortality rate of 30 percent, and an increase in the neonatal mortality rate of 26 percent, compared to the infants of nonsmokers. The overall mortality ratio of late fetal plus neonatal deaths was 1.28 ($P<0.001$). Given the large number of women in the study, and the significant changes in smoking behavior which occurred, they found it possible to consider the effect of a change in smoking

behavior between the beginning of pregnancy and the fourth month on late fetal and neonatal mortality. A statistically significant and dose-related increase in mortality occurred among the infants of mothers who continued to smoke after the fourth month of pregnancy, as compared with the infants of nonsmokers and those of women who smoked prior to the pregnancy but gave up smoking by the fourth month of gestation.

Niswander and Gordon (*63*) reported data from the prospective Collaborative Perinatal Study of the National Institute of Neurological Disease and Stroke. The 39,215 pregnancies registered at 12 university hospitals in the United States were almost equally divided between black and white women. They found a nonsignificant increase in perinatal mortality among the infants of white smokers as compared to those of white nonsmokers; the overall mortality ratio was 1.13 ($P>0.1$). The infants of black smokers, however, had a significantly higher mortality risk than did those of black nonsmokers; the mortality ratio was 1.18 ($P<0.02$). Moreover, a definite dose-response relationship between cigarettes smoked by pregnant mothers and mortality risk was shown for black infants. Black women were noted to smoke significantly fewer cigarettes, on the average, than white women.

Rush and Kass (*82*) found, in a prospective study of 3,276 pregnancies followed at Boston City Hospital, a nonsignificant increase in late fetal plus neonatal mortality rate among the infants of white women who smoked as compared to those of white nonsmokers. However, the infants of black women who smoked had a statistically significant increase in mortality rate compared to the infants of black nonsmokers ($P<0.01$). The overall mortality ratio for black women who smoked was 1.86. The difference in frequency of stillbirth among the infants of smokers and nonsmokers was the primary factor which contributed to the significance of the difference in mortality rates.

Analysis of Previously Reported Studies

Previously reported studies can be divided into two groups: A group in which the late fetal plus neonatal mortality rates for infants born to cigarette smokers were significantly higher than those for the infants born to nonsmokers, and a group in which no significant differences were detected in the mortality rates for the infants born to smokers and nonsmokers. The results of several studies (*14*, *17*, *25*, *42*, *43*, *55*, *84*, *92*) yielded mortality ratios ranging from 1.38 to 1.78. The results of other studies (*20*, *65*, *76*, *85*, *100*, *115*) yielded mortality ratios ranging from 1.01 to 1.06. Both groups contained retrospective and prospective studies of comparable size. The two groups did differ

significantly, however, with regard to control of variables other than cigarette smoking which influence perinatal mortality.

Factors Which Influence Perinatal Mortality Other Than Smoking

Butler and Alberman (*13*), on data from the British Perinatal Mortality Study, employed a logit transformation analysis of variance, and demonstrated that maternal height, age, parity, social class, and severe preeclampsia all had a significant independent effect on late fetal and neonatal mortality. Rumeau-Roquette (*81*) provided evidence that a previous stillbirth or low-birth-weight infant significantly increased the risk of a future stillbirth. Meyer and Comstock (*51*) provided examples of how the differential distribution of smoking and other factors which are related to perinatal mortality, in a population of women, can bias data (e.g., black women have higher perinatal mortality rates than do white women, but black women smoke less than white women do. Hence, nonsmokers will tend to include more black women, and smokers more white women. This will tend to reduce any differences between the groups in mortality rates.) Meyer and Comstock concluded, "Comparisons of mortality rates of smokers' and nonsmokers' babies should be made within subgroups according to parity, socioeconomic status, and other appropriate risk factors, and not separated by birth weight."

In three of the studies in which a significantly higher mortality risk was demonstrated for the infants of smokers, adjustment for other variables was performed. The results indicated that, after such adjustment, a significant independent association between cigarette smoking and infant mortality persisted (*13* and *15*, *17*, *81*). Of the studies which revealed no significant increase in mortality risks for smokers' infants, one (*115*) controlled for race alone. Hence, at least part of the discrepancy in results between the two groups of studies may be explained by a lack of control of variables other than smoking.

Another possible, at least partial, explanation of the discrepancy in results obtained by the two sets of studies is that cigarette smoke may be more harmful to the fetuses of certain women than others. Several developing lines of evidence suggest that this may be the case:

1. Cigarette smoking and socioeconomic background.

Butler, et al. (*15*) noted that when data from the British Perinatal Mortality Study are grouped by social class of the mother's husband, the late fetal plus neonatal mortality ratio for infants of smokers and nonsmokers in the upper social classes I and II is 1.10; the mortality ratio for the entire sample was 1.28. Rush and Kass (*82*) reviewed the British Perinatal Mortality Study, along with several other studies, and noted that all have shown the strongest association between excess infant mortality and cigarette smoking among the infants of those

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mothers with lower socioeconomic status. Comstock and Lundin (*16*) found excess mortality among smokers' infants almost entirely confined to those whose fathers had a grammar school education or less. Several of the studies which revealed no significant difference in mortality among the infants of smokers and nonsmokers were conducted in predominately middle class populations (*20*, *100*, *115*).

2. Cigarette smoking and previous obstetrical experience.

Peterson, et al. (*72*) had rigid criteria for entry into his study population of 7,740 women. He included only those women who previously had healthy infants with a birth weight greater than 2,500 grams. He found a significant decrease in birth weight among smokers' infants, but no significant increase in mortality rates. Rumeau-Roquette (*81*) found that among women who previously had delivered only healthy infants weighing more than 2,500 grams, cigarette smoking was not associated with an increased risk of stillbirth; among those women with a previous stillbirth, smoking was significantly associated with increased risk of a future stillbirth.

3. Cigarette smoking and genetic differences.

The consistent finding that the mortality risk for the infants of black smokers is higher than the risk for the infants of white smokers, even when the socioeconomic background for both is ostensibly similar, suggests that genetic factors also may interact with smoking to produce enhanced risk (*82*, *99*, *115*).

Available evidence suggests that if those women, who are already likely to have small infants for reasons other than smoking, smoke during pregnancy, their infants will be most unfavorably affected. This means that the women in the United States whose infants will be most affected by cigarette smoking are those who have an unfavorable socioeconomic situation, have a history of previously unsuccessful pregnancies, and are black.

Experimental Studies

Studies in Animals

Studies previously reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*) demonstrate that exposure of rabbits and rats to tobacco smoke and to injections of large doses of nicotine resulted in significantly increased late fetal and neonatal mortality. Astrup (*2*) has recently studied the effect of continuous exposure of pregnant rabbits to carbon monoxide on stillbirth rates. He found a significantly higher, dose-related incidence of stillbirths and deaths within the first 24 hours of life among the offspring of the experimental rabbits (table 4).

TABLE 4.—*Effect of carbon monoxide exposure of pregnant rabbits on birth weight and neonatal mortality*

	Group 1, 0 percent COHb	Group 2, 8 to 10 percent COHb	Group 3, 16 to 18 percent COHb
Number of pregnant rabbits	17	14	17
Total number of babies	116	81	123
Stillborn and babies died within first 24 hours	[1] 1	[2] 8	[3] 44
		(P<0.001)	

[1] 1 percent.
[2] 10 percent.
[3] 36 percent.
Source: Astrup, P. (*2*).

Studies in Humans

Some investigators have examined the causes of death among the infants of smokers as compared with those of nonsmokers. Comstock, et al. (*17*) found that infants of smokers died more frequently of asphyxia, atelectasis, and immaturity. Kullander and Källen (*43*) found abruptio placentae significantly increased as a cause of death among smokers' infants. Butler and Alberman (*14*) found little difference in the death rates for the infants of smokers and nonsmokers from isoimmunization and malformations, but higher rates were found for smokers' infants in the groups in which death occurred before or during labor, or in which death resulted from massive pulmonary hemorrhage, or pulmonary infection. As the authors noted, "The latter three are conditions known to be associated with small-for-dates babies." They pointed out that distribution of causes of death in the smoking group could be accounted for almost entirely by the excess of low-birthweight babies. This supports the conclusion that the mechanism which affects birth weight also influences mortality.

SIGNIFICANCE OF THE ASSOCIATION

The following calculation is offered to give some idea of the order of magnitude of increased late fetal and neonatal mortality associated with cigarette smoking during pregnancy. If women who smoked dur-

ing pregnancy in the United States had an elevation in risk of 28 percent for late fetal and neonatal mortality, as demonstrated by Butler, et al. (*15*) for Britain, Scotland, and Wales, and if 20 percent of pregnant women smoked throughout the pregnancy,[1] the higher risk of stillbirth and neonatal death for the infants of mothers who smoke cigarettes during pregnancy would account for approximately 4,600 of the 87,263 stillbirth and neonatal deaths in the United States in 1968.

Late Fetal and Neonatal Death Summary

A strong, probably causal association between cigarette smoking and higher late fetal and infant mortality among smokers' infants is supported by the following evidence:

1. Twelve retrospective and prospective studies have revealed a statistically significant relationship between cigarette smoking and an elevated mortality risk among the infants of smokers. In three of these studies, of sufficient size to permit adjustment for other risk factors, a highly significant independent association between smokng and mortality was established. Part of the discrepancy in results between these studies and those in which a significant association between smoking and infant mortality was not demonstrated may be explained by a lack of adjustment for risk factors other than smoking.
2. Evidence is converging to suggest that cigarette smoking may be more harmful to the infants of some women than others; this may also, in part, explain the discrepancies between the results of the studies in which a significantly higher mortality risk was shown for the infants of smokers compared to those of nonsmokers and the results of those studies in which significant differences in mortality risk were not found.
3. Within groups of similar birth weight, the infants of nonsmokers appear to have a higher mortality risk than do the infants of cigarette smokers. This results from the fact that the infants of nonsmokers within such similar birth weight groups are on the average gestationally less mature than the infants of cigarette smokers. Available evidence indicates that within groups of similar gestational age, infants of lower birth weight experience a higher mortality risk. Since the infants of cigarette smokers are

[1] Based on extrapolation of data on smoking behavior change during pregnancy from the British Perinatal Mortality Study, which probably yields a conservative estimate.

small-for-gestational age, one should expect that if the infants of cigarette smokers and nonsmokers are compared within similar gestational age classes, the infants of cigarette smokers would have the higher mortality rate.

4. The results of recent studies have documented a statistically significant dose-response relationship between the number or amount of cigarettes smoked and late fetal and neonatal mortality.
5. New data suggest that if a woman gives up smoking by the fourth month of pregnancy, she will have the same risk of incurring a fetal or neonatal loss as a nonsmoker.
6. Available evidence strongly supports cigarette smoking as one cause of fetal growth retardation. The causes of excess deaths among the infants of smokers are those associated with small-for-dates babies.
7. Data from experiments in animals have demonstrated that exposure to tobacco smoke or some of its ingredients, such as nicotine or carbon monoxide, results in a significant increase in late fetal and or neonatal deaths.
8. The results of studies in humans have shown that the fetus of a smoking mother may be directly exposed to agents such as carbon monoxide within tobacco smoke, at levels comparable to those which have been shown to produce stillbirth in experimental animals.

Sex Ratio

Although a number of small studies have found a slight, usually statistically nonsignificant, increase in the proportion of female infants born to smokers, the three largest studies of Underwood, et al. (48,505 pregnancies), Butler (15,791 pregnancies), and MacMahon (12,155 pregnancies) have found similar infant sex ratios among both smoking and nonsmoking mothers, with the expected slight excess of males among each (table 5).

Summary

Available evidence strongly indicates that maternal cigarette smoking does not influence the sex ratio of newborn infants.

TABLE 5.—*Proportion of male infants delivered to smoking and nonsmoking mothers*

Author, reference	Pregnancies	Proportion of male infants		Statistical significance
		Smokers	Nonsmokers	
Underwood, et al. (*100*)	48, 505	.518	.519	None.
Butler and Alberman (*14*)	15, 791	.518	.516	Do.
MacMahon, et al. (*49*)	12, 155	.513	.512	Do.
Kullander and Källen (*43*)	6, 363	.515	.501	Do.
Reinke and Henderson [1] (*78*)	3, 156	.498	.517	Do.
Frazier, et al.[1] (*26*)	2, 915	.472	.505	Do.
				(P>0.05)
Kizer (*42*)	2, 095	.502	.493	None.
Herriott, et al. (*36*)	2, 745	.492	.517	Do.
Ravenholt, et al (*77*)	2, 052	.501	.533	P<0.05
Lowe (*46*)	2, 042	.532	.529	None.
Russell, et al. (*83*)	2, 002	.513	.512	Do.

[1] Black women.

Congenital Malformations

Previous epidemiological studies which examined the relationship between cigarette smoking and congenital malformations were reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*). Recently, the authors of the Ontario Perinatal Mortality Study (*66*, *67*), a retrospective study of 51,490 births, reported no difference in malformation rate for the infants of smokers and nonsmokers. The various studies of the association between cigarette smoking and congenital malformation have differed significantly with regard to study design, the type of population sampled, sample size and number of infants with malformations, the definition of malformation, and results (table 6).

Previous experimental work was reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*). The chick embryo has been employed in recent studies. The direct application of nicotine to the embryo results in cephalic hematomas (*26*), malformations of the cervical vertebrae (*93*), and anomalies of the heart (*27*), depending upon dose of nicotine and period of incubation in which exposure occurs. Anomalies of the limbs of chicken embryos can also be induced by exposure of the egg to high levels of carbon monoxide (*4*).

TABLE 6.—*Relative risk of congenital malformation for infants of cigarette smokers and nonsmokers, comparing available studies with regard to study design, study population, sample size, number of infants with malformations, and definition of malformation*

Author, reference	Study design	Study population	Sample size	Infants with malformations	Relative risk SM/NS	Definition of malformations
Lowe (*16*)	Retrospective	Stillborn plus 24-hour deaths.	2,042	23	1.36	Major.
Comstock, et al. (*17*)	...do...	Neonatal deaths	236	37	.31	Major, cause of death.
Yerushalmy (*118*)	Prospective	Infants less than 2,500 g.	695	59	.67	Major.
Ontario Department of Health (*67*)	Retrospective	Stillborn plus 1st-week deaths plus surviving infants.	51,490	1,744	.97	
Butler and Alberman (*14*)	...do...	Stillborn plus neonatal deaths.	7,123	1,382	1.19	Major, cause of death.
Kullander and Källen (*43*)	Prospective	(a) Stillborn plus neonatal deaths plus remainder of deaths to age 1.	137	43	1.25	Major and minor malformations.
		(b) Surviving infants to age 1.	4,903	700	1.06	
Fedrick, et al. (*24*)	Retrospective	(a) [1] Stillborn plus neonatal deaths [1] and deaths to age 7,[1] survivors [2] to age 7.	17,418	86	1.55	(1).
		(b) Neonatal deaths [1] (3-month study).	7,822	204	1.07	(2).

[1] Autopsy-proven congenital cardiac malformation.
[2] Clinically determined congenital heart disease.

Congenital Malformation Summary

Given the considerable variation in study design, study population, sample size, number of affected infants, definition of malformation, and results, no conclusions can be drawn about any relationship between maternal cigarette smoking and congenital malformation at the present time.

Lactation

Introduction

The following section is a review of available evidence which bears upon any interaction between cigarette smoking and lactation. Emphasis is placed upon the relationship of cigarette smoking to the quantity of milk produced, to the presence of constituents of cigarette smoke within the milk, and to effects upon the nursing infant mediated through changes in either the quantity of milk available or the substances within the milk.

Epidemiological Studies

Underwood, et al. (*99*), in a study of 2,000 women from various social and economic strata, observed a definite but statistically insignificant trend toward more frequent inadequacy of breast milk production among those smoking mothers who attempted to nurse compared to nonsmokers.

Mills (*52*), in a study of 520 women, found that among women who indicated either a desire to nurse or no desire to nurse yet continued to nurse beyond 10 days, and who had delivered their first live-born infant, the average period of nursing for mothers who smoked was significantly shorter than for nonsmokers. Moreover, among the 24 mothers who had given up smoking during at least the final 3 months of their pregnancies, the average length of nursing was identical to that of the nonsmokers. There was no significant difference between smokers and nonsmokers with regard to complete inability to nurse their offspring. This study is difficult to interpret because the author did not determine the reason(s) for the discontinuation of nursing among the women.

Experimental Studies

Studies in Animals

Nicotine

Influence on the Lactation Process

Blake and Sawyer (*11*) studied the influence of subcutaneously injected nicotine (4 mg. total over a 5-minute period) upon lactation in the rat. They found that nicotine inhibited the suckling-induced

rise in prolactin. No effect of injected nicotine was demonstrated for oxytocin secretion since milk release was not blocked.

Wilson (*110*) examined the effects of nicotine supplied through drinking water (0.5, 1.0, and 2.0 mg. daily) on the weight gain of nursing rats. Apparently, the nicotine had been available throughout gestation as well, because the author commented on a reduction in litter size among the experimental groups, more or less proportionate to the dose of nicotine; hence, a prenatal effect could not have been distinguished from a postnatal one. Average birth weight was similar for experimental and control groups. No difference in weight gain was seen for any of the groups. The lack of impact on birth weight suggests that dose was lower than that used in other studies.

Presence of Nicotine in the Milk

Hatcher and Crosby (*32*), using a frog bioassay, reported traces of nicotine in cow's milk 24 hours after the intramuscular injection of 5.0 mg./kg. and 5 hours after the injection of 0.5 mg./kg.

Evidence for an Effect Upon the Nursing Offspring

Hatcher and Crosby (*32*) found that 0.5 mg./kg. nicotine injected into nursing cats had no apparent harmful effect upon the kittens. Apparently 4.0 mg./kg. suppressed lactation. Kittens fed the milk from the cow which had been injected with 5.0 mg./kg. nicotine were also apparently unaffected.

Nitrosamines

Mohr (*53*) found that diethylnitrosamine and dibutylnitrosamine, when administered to lactating hamsters, were associated with the development of typical tracheal papillary tumors in the young, suggesting passage of these compounds in the milk. Although diethylnitrosamine and dibutylnitrosamine have not been identified in cigarette smoke, many N-nitrosamines are potent carcinogens, and some of them are present in cigarette smoke (*37*, *79*).

Studies in Humans

Nicotine and/or Tobacco Smoke

Influence on the Lactation Process

Emanuel (*22*) noted no reduction in milk production among 10 wet nurses who were encouraged to smoke seven to 15 cigarettes daily;

some were observed to inhale the smoke. Hatcher and Crosby (*32*) noted that after a mother smoked seven cigarettes within 2 hours, it was difficult to obtain a specimen of breast milk. Perlman, et al. (*71*) found that of 55 women smokers with an adequate milk supply at the beginning of his study, 11 (20 percent) of the women had an inadequate supply at the time of discharge from the hospital. No relationship was reported between the number of cigarettes smoked and the likelihood of developing an inadequate milk supply. The authors' impression was that there was no greater proportion with an inadequate milk supply among smokers than among nonsmokers, but no corroborating data were supplied.

Presence of Nicotine in the Milk

Hatcher and Crosby (*32*) found, using a frog bioassay, that the milk of a woman collected after she had smoked seven cigarettes in 2 hours contained approximately 0.6 mg./liter nicotine. Emanuel (*22*), using a leech bioassay, studied excretion of nicotine in the milk of wet nurses who were encouraged to smoke for the experiment. After the subjects had smoked six to 15 cigarettes over a 1- to 2-hour period, the author found nicotine in their milk 4 to 5 hours after smoking, with a maximum concentration of 0.03 mg./liter. Bisdom (*10*) demonstrated nicotine in the milk of a mother who smoked 20 cigarettes a day. Thompson (*97*) found approximately 0.1 mg./liter of nicotine in the milk of a mother who smoked nine cigarettes a day (plus three pipefuls). Perlman, et al. (*71*), using a Daphnia bioassay, demonstrated nicotine in the milk of all women who smoked in their study. Moreover, they found a direct dose-relationship between concentration of nicotine and the number of cigarettes smoked. No comment is made by the authors on the possible inaccuracy introduced by examining only the residual milk following nursing, but it is well known that the composition of the fore milk and hind milk is different and perhaps the concentration of nicotine also differs.

Evidence for a Clinical Effect Upon the Offspring

Emanuel (*22*) noted that among the infants in his study, loose stools were observed only in the one whose wet nurse had smoked 20 cigarettes in the previous 4 hours. Bisdom (*10*) observed a case of "nicotine poisoning" in a 6-week-old infant whose mother smoked 20 cigarettes a day. The symptoms included: restlessness, vomiting, diarrhea, and tachycardia. Nicotine was demonstrated in the milk, and the symptoms abated when smoking was stopped. Greiner (*30*) also described a case of possible nicotine poisoning in a 3-week-old nursling

whose mother smoked 35 to 40 cigarettes a day. The symptoms included vomiting and loose stools. Following the curtailment of smoking, the symptoms gradually abated over a 3-day period. Perlman, et al. (*71*) noted no effect of smoking on the weight gain of the infants of the smokers in their study. Furthermore, no untoward symptoms were observed. They therefore doubted an effect of smoking on lactation. They noted that the dose received by the infants was beneath the toxic level as computed from adult experience, and this accorded with their clinical observations. The fact that they admitted to the study only women with an apparently adequate milk supply may have affected their results. The authors suggested that perhaps the lack of effect of smoking upon lactation might represent the development of tolerance to nicotine, as both the mother and the offspring had been exposed throughout the pregnancy.

VITAMIN C

Venulet (*105*, *106*, *107*), in a series of studies, demonstrated that the level of vitamin C was reduced in the milk of smoking mothers as compared with nonsmokers. The clinical significance of this observation has not been evaluated.

Lactation Summary

1. The two pertinent epidemiological studies suggest a possible influence of smoking upon the adequacy of milk supply However, with only limited numbers of women and without control of other potentially significant variables, no conclusions can be drawn.
2. Studies in rats have demonstrated that nicotine can interfere with suckling-induced rise in prolactin. The relevance for humans is uncertain.
3. Evidence exists that nicotine passes into breast milk. No clear evidence for an acute effect upon the nursing infant is available. Potential chronic effects have not been studied.
4. New evidence from experiments with mice suggests that nitrosamines, known carcinogens, pass through the milk to suckling young.

Preeclampsia

Previous epidemiological studies of the relationship between cigarette smoking and preeclampsia were reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*) and form the basis of the following statements:

The results of several large prospective and retrospective studies indicate a statistically significant lower incidence of preeclampsia among smoking women (*14*, *43*, *100*). The results of one large retrospective study demonstrated a significant inverse relationship between the incidence of preeclampsia and the number of cigarettes smoked (*100*). When other risk factors, such as parity, social class, maternal weight before the pregnancy, and maternal weight gain during the pregnancy were controlled, smoking women retained a significantly decreased risk of preeclampsia (*21*). The lower risk of preeclampsia for cigarette smoking women has been demonstrated in Britain and Scotland (*14*, *21*, *46*, *83*), The United States (*100*, *118*), Venezuela (*42*), and Sweden (*43*). If a maternal smoker does develop preeclampsia, however, available data suggest that her infant has a higher mortality risk than does the infant of a nonsmoker with preeclampsia (*21*, *83*).

Summary

1. Available evidence indicates that maternal cigarette smokers have a significantly lower risk of developing preeclampsia as compared to nonsmokers.
2. If a woman who smokes cigarettes during pregnancy does develop preeclampsia, her infant has a higher mortality risk than the infant of a nonsmoker with preeclampsia.

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Chapter 6

Peptic Ulcer Disease

Source: 1973 Report, Chapter 5, pages 151 - 164.

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Introduction

Previous epidemiological and experimental studies of the relationship between cigarette smoking and peptic ulcer disease were reviewed in the 1971 and 1972 reports on the health consequences of smoking (*17, 18*) and form the basis of the following summary:

The results of epidemiological studies indicate that cigarette smoking males have an increased prevalence of peptic ulcer disease and a greater mortality from peptic ulcer as compared to nonsmoking males. Among males, the association between cigarette smoking and peptic ulcer disease is stronger for gastric than for duodenal ulcer, but significant for both. For males, cigarette smoking appears to reduce the effectiveness of standard peptic ulcer treatment and to slow the rate of peptic ulcer healing. The relationship between cigarette smoking and the prevalence of and mortality from peptic ulcer disease is less clear for females than for males.

Experimental studies of the effect of cigarette smoking in man, and of the effect of injection and infusion of nicotine in animals, on gastric secretion and motility have produced conflicting results. In dogs, an infusion of nicotine has been found to inhibit pancreatic and hepatic bicarbonate secretion, thus demonstrating a possible link between cigarette smoking and duodenal ulcer.

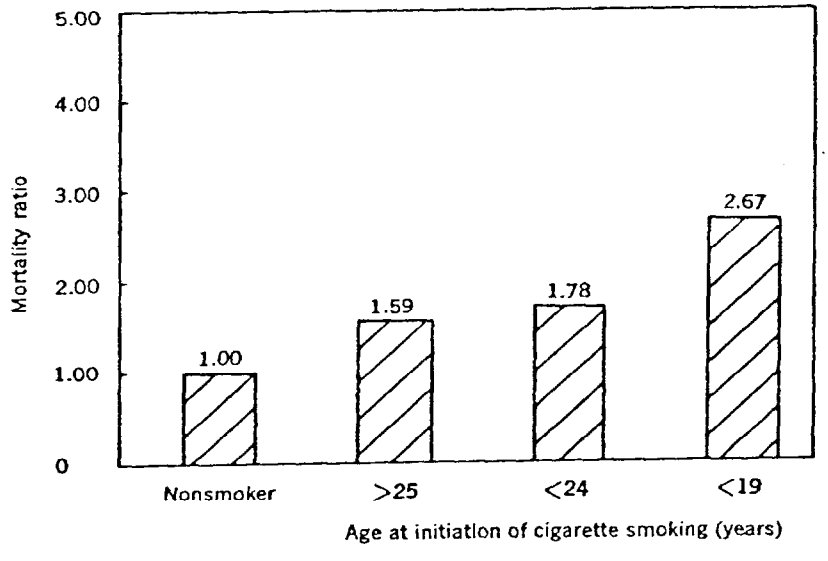
Recently, additional epidemiological, clinical, autopsy, and experimental studies have confirmed the association between cigarette smoking and gastric ulcer mortality and have clarified a mechanism through which cigarette smoking might be linked to duodenal ulcer.

Epidemiological and Clinical Studies

Previous studies of the relationship between peptic ulcer disease and cigarette smoking have been conducted in predominantly white, Western populations. A large prospective epidemiological study is currently being conducted in Japan. From this study, Hirayama (*6*) reported 5-year followup data on 265,118 men and women, aged 40 years and older, representing 91 to 99 percent of the total population in the area of the 29 health districts in which the study was conducted. Both male

and female cigarette smokers experienced higher death rates from gastric ulcer as compared with nonsmokers. The mortality ratio for cigarette smokers was 1.81 for males ($P<0.001$) and 2.15 for females ($P<0.05$). The mortality ratio for smokers (males and females combined) was dose-dependent as measured by age at initiation of smoking (fig. 1). The results of this study, in the context of the genetic and cultural differences between Japanese and Western populations, provide a significant confirmation of the association between cigarette smoking and gastric ulcer mortality.

Figure 1.—Gastric ulcer mortality ratios of Japanese (men and women combined) by age at initiation of cigarette smoking (1966–1970).



SOURCE: Hirayama, T. (6).

Alp, et al. (*1*) conducted a retrospective survey of 638 patients, admitted to two Australian teaching hospitals between 1954 and 1963, with chronic gastric ulcer confirmed by roentgenographic, endoscopic, or surgical examination. The findings in the patients were compared with information available about the South Australian population obtained at census in 1954 and 1961, and with a control group of 233 subjects matched for age and sex with the ulcer patients. Cigarette use, a family history of peptic ulcer, domestic stress, and aspirin and alcohol intake occurred significantly more frequently among ulcer patients. Alp, et al. (*2*) found that after surgical treatment, recurrence of the ulcer was significantly more likely to recur among those patients who continued to smoke, drink, and use aspirin ($P<0.001$).

Fingerland, et al. (*5*) compared the autopsy findings from 765 males with their smoking history. The autopsies were performed without selection during 1965 and 1966 at the University of Hradec Králové, Czechoslovakia. Peptic ulcer was significantly more frequent among male ex-smokers and male lifelong smokers than among male nonsmokers ($P<0.02$). Among males, a dose-response relationship was found between estimated total cigarette consumption and the presence of peptic ulcer at autopsy.

Cooper and Tolins (*4*) reported results from a retrospective study of the relationship between cigarette smoking and postoperative complications among 2,988 males, admitted to 19 Veterans Administration hospitals, for the surgical treatment of duodenal ulcer. Smoking history was obtained for 1,441 of the men, and of these 273 were nonsmokers, 1,018 smoked cigarettes only, and 93 smoked cigarettes plus a pipe and/or cigars. The authors found no evidence of an association between either the number of cigarettes smoked per day, or the number of years of cigarette smoking, and postoperative complications, operative mortality, or length of hospital stay. They emphasized that their results must be viewed with considerable caution and listed several potential sources of bias. In addition, they noted, "* * * that these results apply only to the immediate postoperative findings and do not apply to the long-range effects of smoking upon the patient after surgery for duodenal ulcer disease."

Experimental Studies

Gastric Secretion

Studies in Humans

Morales, et al. (*10, 11*) studied the effect of cigarette smoking on gastric secretion in a group of 312 patients. The patients included 138

with duodenal ulcer, 93 with gastric ulcer, and 81 with other gastrointestinal disorders, who served as controls. Cigarette smoking was significantly more frequent among the patients with peptic ulcer than among the controls.

The chronic effect of smoking on gastric secretion was quite variable. Male smokers among the controls and in the group with duodenal ulcers had a significantly increased baseline acid output as compared with nonsmokers in the same groups ($P<0.05$). After a subcutaneous injection of histamine, only the group of male smokers with gastric ulcers had a significant increase in acid output over the values obtained for nonsmokers in the same group ($P<0.05$). Among the smokers in the control group, the relationship between gastric acid output and the number of cigarettes smoked daily was dose dependent. No such relationship was obtained for either of the two groups with peptic ulcers.

In these experiments, the acute effect of smoking on gastric secretion was slight. In one set of experiments, a group of eight smokers served as its own control. The smoking of two cigarettes prior to collection of gastric juice had no significant effect on acid output as compared to baseline values. After smoking two cigarettes and also receiving a subcutaneous injection of histamine, the patients experienced no significant change in gastric acid output as compared to baseline values; 21 male patients, including members from the groups with ulcers and controls, smoked one cigarette 1 hour after an intravenous infusion of histamine. A transient depression of gastric acid output was noted as compared with the values obtained from nine patients who did not smoke.

Studies in Animals

Konturek, et al. (*8*) studied the effect of intravenous infusion of nicotine on the formation of acute, experimental duodenal ulcers in cats. The authors infused nicotine intravenously in doses comparable to the smoking of four, eight, and 16 cigarettes per hour into cats in whom near maximal gastric acid output had been stimulated with intravenous pentagastrin. The investigators found that nicotine in the two lower doses had no effect upon the gastric acid output stimulated by pentagastrin, but that the highest dose produced a significant decrease in response, due to a fall in both volume and acid concentration. Nicotine alone failed to alter a negligible basal gastric secretion. In control animals (pentagastrin alone), duodenal ulcers were found in eight of 10 animals. Nicotine at the two lower doses, in combination with pentagastrin, produced ulcers in all 26 animals. At the intermediate dose of nicotine, the mean ulcer area was twice that found in

the control group. At the highest dose of nicotine, peptic ulcers appeared in only two of six animals and the area of ulcer was reduced compared to controls.

Shaikh, et al. (*14*) studied the acute and chronic effects of subcutaneously injected nicotine on gastric secretion in rats. Under basal conditions, the volume of gastric secretion was initially depressed, then stimulated, and depressed again as the dose of nicotine was increased. Acid output was decreased over the entire range of nicotine dosage. Pepsin output reflected a similar triphasic response to increasing nicotine doses as did gastric secretory volume. In the absence of nicotine, pentagastrin stimulated gastric volume, acid, and pepsin output. The injection of nicotine, in increasing doses, administered simultaneously with pentagastrin, resulted in a gradual decrease in response for all parameters. Volume of gastric juice, acid output, and pepsin output were all increased significantly by chronic exposure to nicotine alone. Based on an average smoking dose of nicotine, the dose of nicotine employed in the chronic experiments corresponded to the smoking of three to five cigarettes per day.

Thompson, et al. (*16*) extended the study of rats described above by studying the effects of chronic nicotine injections in vagotomized rats and rats with discrete lesions in the hypothalamus. In sham-operated animals, chronic nicotine injections significantly increased baseline volume of gastric juice, acid output, and pepsin output. Following vagotomy, the nicotine response was completely suppressed. Caudal hypothalamic lesions did not influence the response to nicotine in the presence of intact vagus nerves. Anterior hypothalamic lesions, ranging from the anterior hypothalamic area to the ventromedial hypothalamus, blocked the nicotine induced gastric secretory stimulation in the presence of intact vagi. The authors concluded that chronic nicotine-induced gastric secretory stimulation is mediated via anterior hypothalamic activation and intact vagus nerves. The importance of local effects remained uncertain.

Pancreatic Secretion

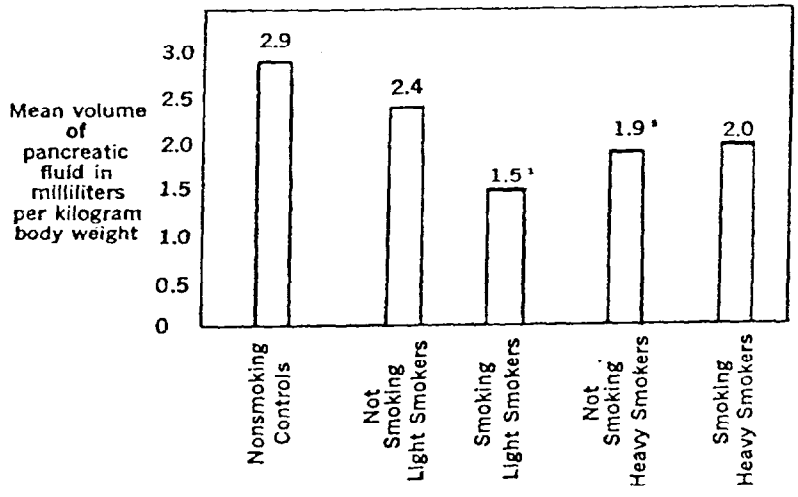
Studies in Humans

Bynum, et al. (*3*) studied the effect of cigarette smoking upon pancreatic secretion in 23 healthy young males and females. Five control male nonsmokers were compared with seven male and two female light smokers (less than one pack of cigarettes per day for less than 3 years) and eight male and one female heavy smokers (more than one pack of

cigarettes per day for more than 3 years). Pancreatic secretion was measured by the double secretin test, using Boots secretin. The experiment was divided into two parts for the smokers: A basal collection period and an experimental period during which the subjects smoked seven nonfiltered cigarettes at the rate of four per hour. Light smokers had basal values for pancreatic secretory volume and bicarbonate output in response to secretin which were not significantly different from controls. After the subjects had smoked, significant depression of both pancreatic volume and bicarbonate output was noted ($P<.001$). Heavy smokers had basal values that were significantly less than in the control subjects ($P<0.01$). Smoking, however, did not further depress the response to secretin (figs. 2 and 3).

Solomon and Jacobsen (*15*) reviewed some possible mechanisms whereby the increased prevalence and mortality from duodenal ulcer among cigarette smokers might be produced. They concluded that evidence from studies in animals, coupled with the findings of Bynum, et al. (*3*), supported the hypothesis that the mechanism active in humans involves impaired neutralization of acid secondary to the inhibition of pancreatic bicarbonate secretion.

Figure 2.—Effect of cigarette smoking on volume of secretin-stimulated pancreatic secretion in humans.

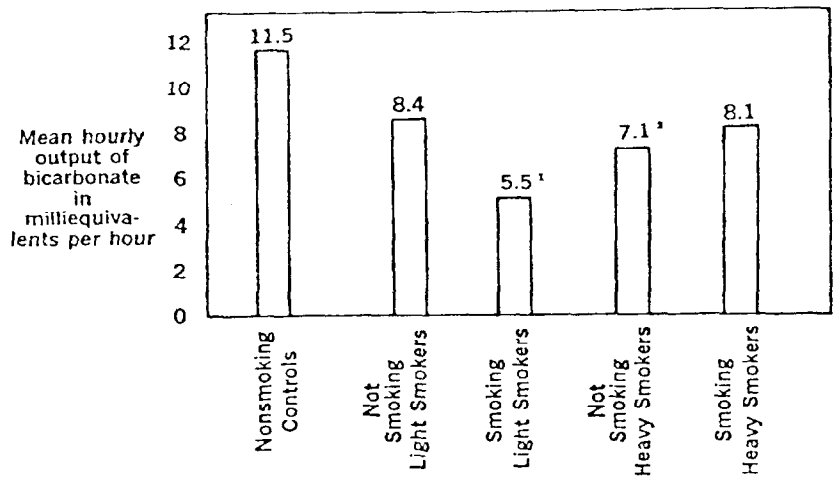


[1] Significantly different from nonsmoking test within group of light smokers ($P<0.001$).

[2] Significantly different from nonsmoking controls ($P<0.01$).

SOURCE: Bynum, et al. (3).

Figure 3.—Effect of cigarette smoking on secretin-stimulated pancreatic bicarbonate output in humans.



[1] Significantly different from nonsmoking test within group of light smokers ($P < 0.001$).

[2] Significantly different from nonsmoking controls ($P < 0.01$).

SOURCE: Bynum, et al. (3).

Studies in Animals

Konturek, et al. (7) extended his research on the mechanism of nicotine-induced inhibition of pancreatic secretion in the dog, using the design previously employed (9). Infused secretin alone led to a sustained increase in pancreatic bicarbonate output. Intravenous nicotine, at all four doses of infused secretin, produced a significant inhibition of pancreatic volume and bicarbonate output ($P<0.05$). Infused nicotine appeared to inhibit competitively the effect of secretin on pancreatic secretion of fluid and bicarbonate. Topical (intraduodenal) nicotine failed to affect significantly the response to infused secretin. Stimulation of endogenous secretin by an acid infusion into the duodenum produced the expected pancreatic secretory response. Nicotine either applied to the duodenal mucosa or injected intravenously significantly inhibited the pancreatic secretory response to endogenous secretin. Nicotine had no significant effect on total pancreatic protein output. Nicotine did not alter the cholecystokinin-induced stimulation of pancreatic secretion. The authors concluded that nicotine may inhibit pancreatic secretion of fluid and bicarbonate both

by a direct effect on pancreatic secretory mechanisms, acting as a competitive inhibitor of secretin, and by a secondary effect on the duodenal mucosa, depressing the endogenous release of secretin by acid.

Robert (*12*) studied the potentiation of active duodenal ulcers by nicotine administration in the rat. Subcutaneous infusion of pentagastrin and carbachol resulted in the dose-dependent formation of duodenal ulcers within 24 hours. Nicotine alone produced no ulcers. Increasing doses of subcutaneously infused nicotine, in combination with the other two agents, resulted in a steadily increasing dose-related incidence and severity of the duodenal ulcers. Robert noted that Konturek, et al. (*9*) found that nicotine inhibited pancreatic and biliary bicarbonate secretion in dogs, and that Thompson, et al. (*16*) found that acute doses of nicotine in rats either depressed or did not alter gastric secretion. He concluded that the most probable mechanism by which nicotine potentiated acute duodenal ulcer formation in the rat was via a suppression of pancreatic secretion.

Robert, et al. (*13*) further tested this hypothesis by infusing acid via the esophagus of rats in doses found to cause duodenal ulcers in one-third of the experimental animals. One group of rats also received a subcutaneous infusion of nicotine. Another received nicotine, but only water was infused via the esophagus; 31 percent of the animals receiving acid but no nicotine had duodenal ulcers; 93 percent of the nicotine-acid group had duodenal ulcers, while none of the nicotine-water group had ulcers. The ulcers in the nicotine-acid group were more numerous, extensive, and deeper than those in the animals which received acid alone.

Summary of Recent Peptic Ulcer Disease Findings

In addition to the findings relating cigarette smoking to peptic ulcer disease, summarized in previous reports on the health consequences of smoking (*17*, *18*) and cited in the introduction to this chapter, recent studies have contributed further to our understanding of the association:

1. The finding of a significant dose-related excess mortality from gastric ulcers among both male and female Japanese cigarette smokers, in a large prospective study, and in the context of the genetic and cultural differences between the Japanese and previously investigated Western populations, confirms and extends the association between cigarette smoking and gastric ulcer mortality.

2. Data from experiments in several different animal species suggest that nicotine potentiates acute duodenal ulcer formation by means of inhibition of pancreatic bicarbonate output.
3. Cigarette smoking has been demonstrated to inhibit pancreatic bicarbonate secretion in healthy young men and women.

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Chapter 7

Involuntary Smoking

Source: 1975 Report, Chapter 4, pages 83 - 112.

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INTRODUCTION

The effects of smoking on the smoker have been extensively studied, but the effects of tobacco smoke on nonsmokers have received much less attention. The 1972 Health Consequences of Smoking (*49*) reviewed the effects of public exposure to the air pollution resulting from tobacco smoke. This exposure has been called "passive smoking" by many authors, but will be referred to in this report as "Involuntary Smoking." The term involuntary smoking will be used to mean the inhalation of tobacco combustion products from smoke-filled atmospheres by the nonsmoker. This type of exposure is, in a sense, "smoking" because it provides exposure to many of the same constituents of tobacco smoke that voluntary smokers experience. It is also "involuntary" because the exposure occurs as an unavoidable consequence of breathing in a smoke-filled environment.

The chemical constituents found in an atmosphere filled with tobacco smoke are derived from two sources — mainstream and sidestream smoke. Mainstream smoke emerges from the tobacco product after being drawn through the tobacco during puffing. Sidestream smoke rises from the burning cone of tobacco. Mainstream and sidestream smoke contribute different concentrations of many substances to the atmosphere for several reasons: Different amounts of tobacco are consumed in the production of mainstream and sidestream smoke; the temperature of combustion differs for tobacco during puffing or while smouldering; and certain substances are partially absorbed from the mainstream smoke by the smoker. The amount of a substance absorbed by the smoker depends on the characteristics of the substance and the depth of inhalation by the smoker. As discussed in the 1972 Report, when the smoker does not inhale the smoke into his lungs, the smoke he exhales contains less than half its original amount of water-soluble volatile compounds, four-fifths of the original nonwater-soluble compounds and particulate matter, and almost all of the carbon monoxide (*15*). When the smoker inhales the mainstream smoke, he exhales into the atmosphere less than one-seventh of the amount of volatile and particulate substances that were originally present in the smoke and also reduces the exhaled CO to less than half its original concentration (*16*). As a result, different concentrations of substances are found in exhaled mainstream smoke depending on the tobacco product, composition of the tobacco, and degree of inhalation by the smoker.

Several minor symptoms (conjunctival irritation, dry throat, etc.) are caused by levels of cigarette smoke encountered in everyday life, and serious allergic-like reactions to cigarette smoke may occur in some sensitive individuals. A major concern, however, about atmospheric contamination by cigarette smoke has been due to the production of significant levels of carbon monoxide. Cigarette smoking in poorly ventilated enclosed spaces may generate carbon monoxide levels above the acceptable 8-hour industrial exposure limits (50 ppm) – set by the American Conference of Government Industrial Hygienists (*1*). Exposure to this level of carbon monoxide even for short periods of time has been shown to reduce significantly the exercise tolerance of some persons with symptomatic cardiovascular disease. There is also some evidence that prolonged exposure to this level of carbon monoxide in combination with a high cholesterol diet can enhance experimental atherosclerosis in animals (Chapter 1, Cardiovascular Diseases).

In the present chapter, the effects of cigarette smoke on the environment and on the nonsmoker in that environment will be examined by reviewing data on (1) the constituents of cigarette smoke measured under various conditions, and (2) the physiologic effects of this "involuntary smoking" on individuals.

CONSTITUENTS OF TOBACCO SMOKE

In a recent workshop on the effects of environmental tobacco smoke on the nonsmoker (*41*), Corn (*14*) presented a compilation adapted from Hoegg (*32*) of some of the substances in mainstream cigarette smoke and the ratio of sidestream to mainstream levels for some of these substances (Table 1). The actual numerical value of the sidestream to mainstream concentration ratio will vary with different types of tobacco tested, but Table 1 gives values generally consistent with those found by others (*34, 42*). Many of these substances including nicotine and carbon monoxide are found in much higher concentrations in sidestream smoke than in mainstream smoke, establishing that the smoke exposure received by both the smoker and nonsmoker due to breathing in a smoke-filled environment differs qualitatively as well as quantitatively from the smoke exposure received by the smoker who inhales through a lighted cigarette. A more comprehensive recent review of the constituents of mainstream and sidestream smoke has also been provided by Schmeltz, et al. (*42*) and Johnson, et al. (*34*).

TABLE 1. – *Comparison of mainstream and sidestream cigarette smoke*[1,2]

	Compound	Mainstream (mg/cig)	Sidestream (mg/cig)	Ratio Sidestream/ Mainstream	Comment
A	General characteristics				
	Duration of smoke production	20 sec	550 sec	27	
	Tobacco burnt	347	411	1.2	
	Particulates, no. per cigarette	1.05×10^{12}	3.5×10^{12}	3.3	
B	Particulate phase				
	[2]Tar (chloroform extract)	20.8	44.1	2.1	
		10.2	34.5	3.4	Filter cigarette
	Nicotine	0.92	1.69	1.8	
		0.46	1.27	2.8	Filter cigarette
	Benzo(a)pyrene	3.5×10^{-5}	13.5×10^{-5}	3.7	
	Pyrene	13×10^{-5}	39×10^{-5}	3.0	
	Total phenols	0.228	0.603	2.6	
	Cadmium	12.5×10^{-5}	45×10^{-5}	3.6	
C	Gases and vapors				
	Water	7.5	298	39.7	3.5 mg of Mainstream and 5.5 mg of Sidestream in particulate phase, rest in vapor phase
	Ammonia	0.16	7.4	46	
	Carbon monoxide	31.4	148	4.7	
	Carbon dioxide	63.5	79.5	1.3	
	Oxides of Nitrogen	0.014	0.051	3.6	

[1] Adapted from Hoegg, U.R. (*31, 32*).

[2] For 35 ml puff volume, 2 sec puff duration, one puff per minute and 23 or 30 mm butt length and 10 percent tobacco moisture. Source: Corn, M. (*14*).

A number of other researchers have attempted to measure the levels of some of the substances in cigarette smoke encountered in everyday situations (Table 2). They have also tried to determine the factors controlling the atmospheric concentrations of these substances as well as the amount absorbed by nonsmokers under these conditions. Carbon monoxide, nicotine, benzo(a)pyrene, acrolein, and acetaldehyde have been of particular concern.

Carbon Monoxide

Levels of carbon monoxide (CO), a major product of tobacco combustion, have been studied in a variety of situations, and concentrations ranging from 2 to 110 ppm have been measured (Table 2). The major determinants of the CO levels in these situations are size of the space in which the smoking occurs (dilution of CO), the number and type of tobacco products smoked (CO production), and the amount and effectiveness of ventilation (CO removal).

The type of tobacco product smoked is important as a determinant of CO exposure because it has been found that mainstream smoke from regular and small cigars contains more CO pre puff and per gram of tobacco burned than filtered or unfiltered cigarettes (*8*). This greater production of CO by cigars was confirmed by Harke (*23*). He measured the CO produced by 42 cigarettes, 9 cigars, and 9 pipefuls of tobacco, each product evaluated separately but under the same room conditions. The cigars produced the highest CO level (60 ppm).

In addition to the effect of type of tobacco product on CO levels, data on the effects of room size, amount of tobacco burned, and ventilation are included in Table 2. Only under conditions of unusually heavy smoking and poor ventilation did CO levels exceed the maximum permissible, 8-hour industrial exposure limit of 50 ppm CO (*1*); however, even in cases where the ventilation was adequate, the measured CO levels did exceed the maximum acceptable ambient level of 9 ppm (*18*).

Harke (*27*) also showed that in small enclosed ventilated spaces (an automobile) the CO level is determined more by the number of cigarettes being smoked at one given time than by the cumulative number of cigarettes that have been smoked; also the CO level decreases rapidly once the smoking stops.

TABLE 2. – *Measurements of constituents released by the combustion of tobacco products in various situations*

[Cig = cigarettes; – = unknown; TPM = total particulate matter]

Reference, Location, and Dimensions If Known	Ventilation	Amount of Tobacco Burned	Constituents
Harke, H.-P., et al. (27)			
Mid-size European car, engine off, in wind tunnel at 50 km/hr wind speed	None	9 cig	30 ppm CO
	Air jets open & blower off	6 cig	20 ppm CO
	Air jets open & blower on	6 cig	10 ppm CO
Mid-size European car, engine off, in wind tunnel at zero km/hr wind speed	None	9 cig	110 ppm CO
	None	6 cig	80 ppm CO
	Air jets open & blower on	6 cig	8-10 ppm CO
Harke, H.-P., Peters, H. (28)			
Car in traffic	None	4 cig	21.4 ppm CO
Srch, M. (45)			
Car, engine off– 2.09 m^3	None	10 cig in 1 hr	90 ppm CO, Smokers 10% COHb Nonsmokers 5% COHb
Seiff, H.E. (44)			
Intercity buses	15 air changes per hr	23 cig (burning continuously)	33 ppm CO (at driver's seat)
		3 cig (burning continuously)	18 ppm CO (at driver's seat)

TABLE 2. – *Measurements of constituents released by the combustion of tobacco products in various situations – Continued*

[Cig = cigarettes; – = unknown; TPM = total particulate matter]

Reference, Location, and Dimensions If Known	Ventilation	Amount of Tobacco Burned	Constituents
U.S. Dept. Transportation, et al. (*48*)			
Airplane flights:			
Overseas–100% filled	15-20 air changes per hr	–	2-5 ppm CO, <.120 mg/m^3 TPM
Domestic–66% filled	do.	–	<2 ppm CO, <.120 mg/m^3 TPM
Cano, J.P., et al. (*11*)			
Submarines–66 m^3	Yes	157 cig per day	<40 ppm CO, 32 μg/m^3 Nicotine
		94-103 cig per day	<40 ppm CO, 15-35 μg/m^3 Nicotine
Godin, G., et al. (*21*)			
Ferry boat compartments:			
Smoking	–	–	18.4 ±8.7 ppm CO
Nonsmoking	–	–	3.0±2.4 ppm CO
Theater:			
Foyer	–	–	3.4±0.8 ppm CO
Auditorium	–	–	1.4±0.8 ppm CO
Bridge, D.P., Corn, M. (*7*)			
Party rooms:			
145 m^3	7 air changes per hr	50 cig & 17 cigars in 1.5 hr	7 ppm CO
101 m^3	10.6 air changes per hr	63 cig & 10 cigars in 1.5 hr	9 ppm CO

TABLE 2. – *Measurements of constituents released by the combustion of tobacco products in various situations – Continued*

[Cig = cigarettes; – = unknown; TPM = total particulate matter]

Reference, Location, and Dimensions If Known	Ventilation	Amount of Tobacco Burned	Constituents
Harke, H.-P., et al. (*25*)			
Room–38.2 m^3	None	30 cig per 13 min (by machine)	64 ppm CO, 510 $\mu g/m^3$ Nicotine .46 mg/m^3 Acrolein 6.5 mg/m^3 Acetaldehyde
		5 cig per 13 min (by machine)	11.5 ppm CO, 60 $\mu g/m^3$ Nicotine, ..07 mg/m^3 Acrolein, 1.3 mg/m^3 Acetaldehyde
Harke, H.-P. (*24*)			
Office Bldg	Air conditioned	–	<5 ppm CO
Office Bldg	Not air conditioned	–	<5 ppm CO
Room–78.3 m^3	–	3 smokers	15.6 ppm CO
Harke, H.-P., (*23*)			
Room–57 m^3	None	42 cig (by machine)	50 ppm CO, 530 $\mu g/m^3$ Nicotine
	7.2 air changes per hr	42 cig do.	10 ppm CO, 120 $\mu g/m^3$ Nicotine
	8.4 air changes per hr	42 cig do.	<10 ppm CO, <100 $\mu g/m^3$ Nicotine
	None	9 cigars do.	60 ppm CO, 1040 $\mu g/m^3$ Nicotine
	7.2 air changes per hr	9 cigars do.	20 ppm CO, 420 $\mu g/m^3$ Nicotine
	None	9 pipes do.	10 ppm CO, 520 $\mu g/m^3$ Nicotine
	7.2 air changes per hr	9 pipes do.	<10 ppm CO, <100 $\mu g/m^3$ Nicotine

TABLE 2. – *Measurements of constituents released by the combustion of tobacco products in various situartions – Continued*
[Cig = cigarettes; – = unknown; TPM = total particulate matter]

Reference, Location, and Dimensions If Known	Ventilation	Amount of Tobacco Burned	Constituents
Harke, H.-P. (*23*) Room – 170 m^3	None	105 cig	30 ppm CO, Smokers 7.5% COHb Nonsmokers 2.1% COHb
	1.2 air changes per hr	107 cig	5 ppm CO, Smokers 5.8% COHb Nonsmokers 1.3% COHb
	2.3 air changes per hr	101 cig	75 ppm CO, Smokers 5.0% COHb Nonsmokers 1.6% COHb
Anderson, G., Dalhamn, T. (*3*) Room – 80 m^3	6.4 air changes per hr	46 cig & 3 pipefuls	4.5 ppm CO, 377 $\mu g/m^3$ Nicotine, 3.0 mg/m^3 TPM
Russell, M.A.H., et al. (*40*) Room – 43 m^3	None	80 cig & 2 cigars per hr	38 ppm CO, Smokers 9.6% COHb Nonsmokers 2.6% COHb
Hammsen, H., Effenberger, E. (*30*) Room – 93 m^3	None	62 cig in 2 hrs	80 ppm CO, 5200 $\mu g/m^3$ Nicotine
Hoegg, U.R. (*31, 32*) Sealed test chamber – 25 m^3	None	4 cig	12.2 ppm CO, 2.28 mg/m^3 TPM
		8 cig	25.6 ppm CO, 5.39 mg/m^3 TPM
		16 cig	47.0 ppm CO, 11.41 mg/m^3 TPM
		24 cig	69.8 ppm CO, 16.65 mg/m^3 TPM

One must be careful when using the levels recorded in Table 2 as measures of individual exposure because the CO levels were usually measured at points several feet from the nearest smoker and probably would have been higher if measured at points corresponding to the position of a person sitting next to someone actively smoking (*17, 35*). In addition, it is the CO absorbed by the body that causes the harmful effects and not that which is measured in the atmosphere. This absorption can vary from individual to individual, depending on factors such as duration of exposure, volume of air breathed per minute, and cardio-respiratory function.

Several investigators have tried to determine the amount of carbon monoxide absorbed in involuntary smoking situations by measuring changes in carboxyhemoglobin levels in nonsmokers exposed to cigarette smoke-filled environments. Anderson and Dalhamn (*3*) were unable to find any change in the COHb levels of nonsmokers in a well ventilated room where the CO level was 4.5 ppm. When Harke (*23*) studied nonsmokers under similar conditions (good ventilation and less than 5 ppm CO), he was able to show an increase in COHb level from 1.1 to 1.6 percent: without ventilation the CO levels rose to 30 ppm and the COHb level increased from .9 to 2.1 percent in 2 hours. Russell, et al. (*40*) also found that COHb levels increased from 1.6 to 2.6 percent in nonsmokers exposed to a smoke-filled room where the CO level was measured at 38 ppm: however, he cautioned that nearly all persons in the room felt that the conditions were worse than those experienced in most social situations.

Stewart, et al. (*46*) measured COHb levels in a group of nonsmoking blood donors from several cities and found that 45 percent exceeded the Clean Air Act's Quality Standard of 1.5 percent with the 90 percent range as high as 3.7 percent for individual cities (Table 3). These levels represent the total CO exposure from all sources, involuntary smoking, and other sources of pollution as well as establishing the levels which would be added to any new involuntary smoking exposure.

Increases in the COHb levels of this magnitude are probably functionally insignificant in the healthy adult, but in persons with angina pectoris, any reduction of oxygen-carrying capacity is of great importance. In this disease, the volume of blood able to be pumped through the diseased coronary artery is already unable to meet the demands of the heart muscle under exercise stress. Aronow, et al. (*4*) examined the effect of exposure to carbon monoxide on persons with angina pectoris. They exercised persons with angina

TABLE 3. – *Median percent carboxyhemoglobin (COHb) saturation and 90 percent range for nonsmokers by location*

Location	Nonsmokers		No. of Nonsmokers	Percent of Nonsmokers With COHb >1.5%
	Median	Range		
Anchorage	1.5	0.6 – 3.2	152	56
Chicago	1.7	1.0 – 3.2	401	74
Denver	2.0	0.9 – 3.7	744	76
Detroit	1.6	0.7 – 2.7	1,172	42
Honolulu	1.4	0.7 – 2.5	503	39
Houston	1.2	0.6 – 3.5	240	30
Los Angeles	1.8	1.0 – 3.0	2,886	76
Miami	1.2	0.4 – 3.0	398	33
Milwaukee	1.2	0.5 – 2.5	2,720	26
New Orleans	1.6	1.0 – 3.0	159	59
New York	1.2	0.6 – 2.5	2,291	35
Phoenix	1.2	0.5 – 2.5	147	24
St. Louis	1.4	0.9 – 2.1	671	35
Salt Lake City	1.2	0.6 – 2.5	544	27
San Francisco	1.5	0.8 – 2.7	660	61
Seattle	1.5	0.8 – 2.7	535	55
Vermont, New Hampshire	1.2	0.8 – 2.1	959	18
Washington, D.C.	1.2	0.6 – 2.5	850	35

Source: Stewart, R.D., et al. (*46*).

pectoris before and after exposure to carbon monoxide. The average amount of exercise that was able to be performed before a person developed chest pain was significantly shortened from 226.7 seconds before exposure to 187.6 seconds after CO exposure. This change occurred after a 2-hour exposure to 50 ppm CO and with an increase in COHb level from 1.03 percent to 2.68 percent; these COHb levels are within the range produced by involuntary smoking.

These data indicate that exposure to CO at levels found in some involuntary smoking situations may well have a significant impact on the functional capacity of persons with angina pectoris. Carbon monoxide has also been shown to decrease cardiac contractility in persons with coronary heart disease at COHb levels similar to those produced due to involuntary smoking situations (*5*). It is reasonable to assume that any significant CO exposure to the diseased heart reduces its functional reserve.

Nicotine

Nicotine in the atmosphere differs from CO in that it tends to settle out of the air with or without ventilation (thereby decreasing its atmospheric concentration), whereas the CO level will remain constant until the CO is removed. The concentrations of both substances are decreased substantially by ventilation. As can be seen from data in Table 2, under conditions of adequate ventilation neither exceeds the maximum threshold limit values for industrial exposure (nicotine, 500 $\mu g/m^3$; CO, 50 ppm, *1*); whereas in conditions without ventilation, smoking produces very high concentrations of both (nicotine, up to 1,040 $\mu g/m^3$; CO, 110 ppm).

Nicotine in the environment is of concern because nicotine absorbed by cigarette smokers is felt to be one factor contributing to the development of atherosclerotic cardiovascular disease. Several researchers have attempted to measure the amount of nicotine absorbed by nonsmokers in involuntary smoking situations. Cano, et al. (*11*) studied urinary excretion of nicotine by persons on a submarine. Despite very low levels measured in the air (15 to 32 $\mu g/m^3$), nonsmokers did show a small rise in nicotine excretion; however, the amount excreted was still less than 1 percent of the amount excreted by smokers. Harke (*23*) measured nicotine and its metabolite cotinine in the urine of smokers and nonsmokers exposed to a smoke-filled environment and reported that nonsmokers excreted less than 1 percent of the amount of nicotine and cotinine excreted by smokers. He feels that at this low level of absorption nicotine is unlikely to be a hazard to the nonsmoker.

Other Substances

In two studies environmental levels of the experimental carcinogen benzo(a)pyrene were measured. Galuskinova (*20*) found levels of benzo(a)pyrene from 2.82 to 14.4 mg/m^3 in smoky restaurants, but it is not clear how much of this was due to cooking and how much was due to smoking. In a study of the concentration of benzo(a)pyrene in the atmosphere of airplanes (*48*), only a fraction of a microgram per cubic meter was detected. The effect of chronic exposure to very low levels of this carcinogen has not been established for humans.

Acrolein and acetaldehyde have also been measured in smoke-filled rooms (*25*, Table 2) and may contribute to the eye irritation commonly experienced in these situations.

EFFECTS OF EXPOSURE TO CIGARETTE SMOKE

Cardiovascular Effects of Involuntary Smoking

The effects of cigarette smoking on the cardiovascular system of the smoker are well established, but very little is known about the cardiovascular response of the nonsmoker to cigarette smoke. Harke and Bleichert (*26*) studied 18 adults (11 smokers and 7 nonsmokers) in a room 170 m^3 large in which 150 cigarettes were smoked or allowed to burn in ashtrays for 30 minutes. They noted that the subjects who smoked during the experiment had a significant lowering of skin temperature and a rise in blood pressure. Nonsmokers who were exposed to the same smoke-contaminated environment showed no change in either of these parameters. Luquette, et al. (*36*) performed a similar experiment with 40 children exposed alternately to smoke-contaminated and clean atmospheres, but otherwise under identical experimental conditions. They found that exposure to the smoke caused increases in heart rate (5 beats per minute) and in systolic (4 mm Hg) and diastolic (5 mm Hg) blood pressure. The differences in results between these studies may be due, in part, to the age of the subjects – i.e., children may be more sensitive to the cardiovascular effects of involuntary smoking than adults, or the increase in heart rate and blood pressure may be due to a difference between children and adults in the psychologic response to being in a smoke-filled atmosphere.

Effects of Carbon Monoxide on Psychomotor Tests

Carbon monoxide from tobacco smoke, automobile exhaust, and industrial pollution is an important component of air pollution. There has been some concern over the effect of relatively low levels of carbon monoxide on psychomotor functions (the ability to perceive and react to stimuli), especially those functions related to driving an automobile (Table 4).

Carbon monoxide levels occasionally reached in some involuntary smoking situations result in measurable cognitive and motor effects, but these effects generally are measurable only at the threshold of stimuli perception. One study (Wright, et al., (*50*)) found that the safe driving habits measured on a driving simulator did not improve as much with practice in a group exposed to CO as did the habits of a control group. Another study (*37*) with a different experimental design but at the same levels of CO did not find any effect on complex psychomotor activity such as driving a car. Thus, the role of CO alone in motor vehicle accidents remains unclear. The effect on judgement and reactions of CO in combination with factors such as fatigue and alcohol, conditions known to influence judgement and reaction time, has not been determined.

Pathologic Effects of Exposure to Cigarette Smoke

The effect of involuntary smoking on an individual is determined not only by the qualitative and quantitative aspects of the smoke-filled environment, but also largely by the characteristics of the individual. Reactions may vary with age as well as with the sensitivity of an individual to the components of tobacco smoke. The severity of possible effects range from minor eye and throat irritations experienced by most people in smoke-filled rooms, to the anginal attacks of some persons with cardiovascular disease.

The minor symptomatic irritation experienced by nonsmokers in a smoke-filled environment is influenced by the humidity of the air as well as the concentration of irritating substances found in the atmosphere. Johansson and Ronge (*33*) have shown that irritation due to cigarette smoke is maximal in warm, dry air and decreases with a small rise in relative humidity. A change from acceptable to unpleasant was reported at 4.7 mg/m^3 of particulate matter for nonsmokers and eye irritation was noted at 9 mg/m^3 for both smokers and nonsmokers. The authors concluded that a ventilation rate of 12 $m^3/hr/cig$ was necessary to avoid eye irritation and 50 $m^3/hr/cig$ was necessary to avoid unpleasant odors.

TABLE 4.– *Effects of carbon monoxide on psychomotor functions*

Reference	Test or Measurement	CO level (ppm)	COHb level (Percent)	Effect
McFarland, R.A. (*37*)	Ability of drivers to stay between two-lane markers while being permitted only brief glimpses of the road		6	None
			11	None
			17	None
Ray, A.M., Rockwell, T.H. (*39*)	Reaction time to car taillights		10	Prolonged
McFarland, R.A. (*38*)	Performance of two tasks at same time	700	17	None
	Dark adaptation and glare recovery	700	17	None
	Peripheral vision at 10° and 30°	700	17	None
	Peripheral vision at 20°	700	17	Decreased
	Depth perception	700	17	None
Stewart, R.D., et al. (*47*)	Time perception	500	20	None

TABLE 4. – *Effects of carbon monoxide on psychomotor functions – Continued*

Reference	Test or Measurement	CO level ppm	COHb level (Percent)	Effect
Fodor, G.G., Winneke, G. (19)	Attentiveness to auditory stimuli	50 x 5 hrs.	2-5	Decreased
	Flicker fusion	50 x 5 hrs.	2-5	No change
	Speed of motor performance	50 x 5 hrs.	2-5	No change
	Perception of complex visual patterns	50 x 5 hrs.	2-5	Improved
Schulte, J.H. (43)	Cognitive function	100	5	Decreased
	Reaction time		20	No change
Bender, W., et al. (6)	Threshold for temporal resolution of visual stimuli	100	7.25	Raised
	Manual dexterity	100	7.25	Decreased
	Learning meaningless syllables	100	7.25	Decreased
	Retention of 10 syllables for 1 hr	100	7.25	No change
Groll-Knapp, E., et al. (22)	Attentiveness to auditory stimuli	50 100 150		Deterioration at 50 ppm, worse at 100 ppm, worst at 150 ppm
Wright, G., et al. (50)	Reaction time		6.3	Prolonged
	Glare recovery		6.3	Prolonged
	Careful driving habits		6.3	Failure to improve with practice

Two government sponsored studies have attempted to evaluate the degree of minor irritation due to cigarette smoke experienced by bus and plane passengers. The U.S. Department of Transportation (*44*) studied the environment on two ventilated buses – one with simulated unrestricted smoking and another with simulated smoking limited to the rear 20 percent of the seats. In one bus, lighted cigarettes were placed at every other seat (23 cigarettes) to simulate a bus filled with smokers. In the other bus, cigarettes were placed only in the rear 20 percent of the bus (five cigarettes) to simulate a bus where smoking was limited to the rear 20 percent of the seats. When smoking was limited, the CO level at the driver's seat was only 18 ppm (ambient air 13 ppm) compared to the level of 33 ppm (ambient air 7 ppm) measured in the unrestricted smoking situation. Four of the six subjects seated in the bus reported eye irritation during the unrestricted smoking simulation. None of the six subjects reported any eye irritation in the restricted smoking situation (not even those seated in the rear 20 percent of the bus).

Several Federal agencies (*48*) cooperated to survey the symptoms experienced by travelers on both military and commercial aircraft. They distributed a questionnaire to passengers on 20 military and 8 commercial flights; 57 percent of the passengers on the military flights and 45 percent of the passengers on the commercial flights were smokers. The planes were well ventilated and CO levels were always below 5 ppm with low levels of other pollutants as well. In spite of the low level of measurable pollution, over 60 percent of the nonsmoking passengers and 15 to 22 percent of the smokers reported being annoyed by the other passengers' smoking. Seventy-three percent of the nonsmoking passengers on the commercial flights and 62 percent of the nonsmoking passengers on the military flights suggested that some remedial action be taken; 84 percent of those suggesting remedial action felt that segregating the smokers from nonsmokers would be a satisfactory solution. These feelings were even more prevalent among those nonsmokers who had a history of respiratory disease.

Children have been found to have a higher incidence of respiratory infections than adults and are thought to be more sensitive to the effects of air pollution due to their greater minute ventilation per body weight than adults. Several researchers have investigated the effects of parental smoking on the health of children. Cameron, et al. conducted two telephone surveys of Detroit families to determine the relationship between children's respiratory illness and parental smoking habits. In the first survey (*9*) they found a statistically significant relationship between the prevalence of

children's respiratory infection and parental smoking habits only when all children under 16 were considered (not when only those under 9 or under 5 were considered). In a larger survey of the same city (*10*) they found a relationship between parental smoking and prevalence of respiratory illness in the 10- to 16-year age group and in the birth to 5-year age group. Neither study controlled for smoking by the children which might be a factor in the 10- to 16-year age group or for socioeconomic status which has an effect on both smoking habits and illness. However, the data were consistent with a higher prevalence of respiratory disease in families where there are smokers than in nonsmoking families.

Colley (*12*) also found a relationship between parental smoking habits and the prevalence of respiratory illness in the children. He found an even stronger relationship between parental cough and phlegm production and respiratory infections in children. He postulates this latter relationship to result from the greater infectivity of these parents due to their cough and phlegm production. The relationship between parental cigarette smoking and respiratory infection in their children would then occur because cigarette smoking caused the parents to cough and produce phlegm and would not be indicative of a direct effect of cigarette smoke-filled air on the children.

Harlap and Davies (*29*) studied infant admissions to Hadassah Hospital in West Jerusalem and found a relationship between admissions for bronchitis and pneumonia in the first year of life and maternal smoking habits during pregnancy. Data on maternal smoking habits after the birth of the child were not obtained, but it can be assumed that most of the mothers who smoked during pregnancy continued to smoke during the first year of the infant's life. A relationship between infant admission and maternal smoking habits was demonstrable only between the sixth and ninth months of infant life and was more pronounced during the winter months (when the effect of cigarette smoke on the indoor environment would be greatest). Mothers who smoke during pregnancy are known to have infants with a lower average birth weight than the infants of nonsmoking mothers. The relationship between maternal smoking and their infants' admission to the hospital found in this study was greater for low birth weight infants, but was also found for normal birth weight infants (Table 5) (*29*). Harlap and Davies (*29*) demonstrated a dose-response relationship for maternal smoking and infant admission for bronchitis and pneumonia; however, they also found a relationship between maternal smoking and infant admissions for poisoning and injuries. This may indicate a bias in the study

TABLE 5.– *Admission rates (per 100 infants) by diagnosis, birth weight, and maternal smoking*

Diagnosis	Birth weight (g)						Total (including unknown)	
	<2,999		3,000 - 3,499		3,500+			
	S (297)	NS (2,326)	S (415)	NS (4,098)	S (264)	NS (3,195)	S (986)	NS (9,686)
Bronchitis and pneumonia	19.2	12.3	9.6	8.2	12.1	9.0	13.1	9.5
All other	22.6	19.9	14.5	14.6	15.2	13.3	16.9	15.5
Total	41.8	32.2	24.1	22.8	27.3	22.3	30.0	24.9

NOTE. – S=Smokers; NS=Nonsmokers.
Source: Harlap, S., Davies, A.M. (29).

due to relationships which may exist between smoking and factors such as parental neglect or socioeconomic class. In addition, hospital admission rates may not be an accurate index of infant morbidity.

Colley, et al. (*13*) studied the incidence of pneumonia and bronchitis in 2,205 children over the first 5 years of life in relation to the smoking habits of both parents. They found that a relationship between parental smoking habits and respiratory infection in children occurred only during the first years of life (Table 6). They also showed a relationship between parental cough and phlegm production and infant infection (Table 6) which was found to be independent of the effect of parental smoking habits. The relationship between parental smoking and infant infection was greater when both parents smoked and increased with increasing number of cigarettes smoked per day. The relationship persisted after social class and birth weight had been controlled for.

Thus, respiratory infections during the first year of life are closely related to smoking habits independent of parental symptoms, social class, and birth weight. Because of the dose-response relationship between parental smoking and infant respiratory infection established by Colley, et al. (*13*), it is reasonable to suspect that cigarette smoke in the atmosphere of the home may be the cause of these infections; however, other factors such as parental neglect may also play a role.

The above studies examined the effects of involuntary smoking on relatively healthy people. A substantial proportion of the U.S. population suffers from chronic cardiovascular and pulmonary diseases, however, and they represent the segment of the population most seriously jeopardized by conditions found in involuntary smoking situations. In Chapter 1 of this report (Cardiovascular Diseases) evidence was presented which showed that levels of CO sometimes experienced in smoke-filled environments (50 ppm) are capable of significantly decreasing the exercise tolerance of persons with angina pectoris and intermittent claudication. In addition, these levels of CO have been shown to decrease cardiac contractility and to raise left ventricular end-diastolic pressure (an indication of heart failure) in persons with cardiovascular disease.

Persons with chronic bronchitis and emphysema have considerable excess mortality under conditions of severe air pollution. In smoke-filled environments levels of CO and several other pollutants may be as high or higher than occur during air pollution emergencies. The effects of short-term exposure of persons with chronic obstruc-

TABLE 6. – *Pneumonia and bronchitis in the first 5 years of life by parents' smoking habit and morning phlegm*

Year of Followup	Annual incidence of pneumonia and bronchitis per 100 children (Absolute numbers in parentheses)									
	Both nonsmokers		One smoker		Both smokers		Both ex-smokers or one ex-smoker or smoking habit changed		All	
	N	O/B	N	O/B	N	O/B	N	O/B	N	O/B
1	7.6 (343)	10.3 (29)	10.4 (424)	14.8 (128)	15.3 (339)	23.0 (139)	8.2 (546)	13.2 (129)	10.1 (1,652)	16.7 (425)
2	8.1 (322)	8.3 (36)	7.1 (365)	15.5 (129)	8.7 (286)	9.2 (152)	6.5 (599)	10.7 (159)	7.4 (1,572)	11.3 (476)
3	6.9 (305)	8.1 (37)	10.5 (353)	9.4 (107)	7.9 (242)	11.0 (154)	8.2 (661)	11.6 (173)	8.4 (1,561)	10.6 (471)
4	8.0 (287)	11.1 (36)	7.5 (306)	10.8 (102)	7.6 (236)	11.6 (121)	8.2 (695)	9.1 (187)	7.9 (1,524)	10.3 (446)
5	6.7 (285)	14.7 (34)	5.6 (267)	9.4 (107)	3.9 (208)	10.6 (132)	6.4 (737)	7.3 (219)	5.9 (1,497)	9.1 (492)

NOTE. – N=neither with winter morning phlegm. O/B=one or both with winter morning phlegm.
Source: Colley, J.R.T., et al. (*13*).

tive bronchopulmonary disease (COPD) to these conditions have not been evaluated. Persons with COPD are also possibly at increased risk to CO exposure because of their low alveolar Po_2. Due to the reduced amount of oxygen available to compete with the CO for hemoglobin binding sites, these persons might experience a carboxyhemoglobin to oxyhemoglobin ratio higher than those in healthy subjects under the same conditions of CO exposure. The retention of CO may also be prolonged due to both this increased binding of CO to hemoglobin under low alveolar Po_2 and decreased ventilatory capacity to excrete CO.

In summary, the effects of cigarette smoke on healthy nonsmokers consists mainly of minor eye and throat irritation. However, people with certain heart and lung diseases (angina pectoris, COPD, allergic asthma) may suffer exacerbations of their symptoms as a result of exposure to tobacco smoke-filled environments. These effects are dependent on the degree of individual exposure to cigarette smoke which is determined by proximity to the source of the tobacco smoke, the type and amount of tobacco product smoked, conditions of room size and ventilation as well as the amount of time the individual spends in the smoke-filled environment, and his physiologic condition at the time of exposure.

SUMMARY

1. Tobacco smoke can be a significant source of atmospheric pollution in enclosed areas. Occasionally under conditions of heavy smoking and poor ventilation, the maximum limit for an 8-hour work exposure to carbon monoxide (50 ppm) may be exceeded. The upper limit for CO in ambient air (9 ppm) may be exceeded even in cases where ventilation is adequate. For an individual located close to a cigarette that is being smoked by someone else, the pollution exposure may be greater than would be expected from atmospheric measurements.

2. Carbon monoxide, at levels occasionally found in cigarette smoke-filled environments, has been shown to produce slight deterioration in some tests of psychomotor performance, especially attentiveness and cognitive function. It is unclear whether these levels impair complex psychomotor activities such as driving a car. The effects produced by CO may become important when added to factors such as fatigue and alcohol which are known to have an effect on the ability to operate a motor vehicle.

3. Unrestricted smoking on buses and planes is reported to be annoying to the majority of nonsmoking passengers, even under conditions of adequate ventilation.

4. Children of parents who smoke are more likely to have bronchitis and pneumonia during the first year of life, and this is probably at least partly due to their being exposed to cigarette smoke in the atmosphere.

5. Levels of carbon monoxide commonly found in cigarette smoke-filled environments have been shown to decrease the exercise tolerance of patients with angina pectoris.

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Chapter 8

Allergy

Source: 1972 Report, Chapter 7, pages 99 - 116.

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INTRODUCTION

As early as 1886 reference was made to an entity called "tobacco asthma" (*64*). Subsequently, controversy has arisen over whether tobacco smoking causes clinical allergy (*61*) and whether such tobacco allergy is associated with the major smoking-related diseases (*25, 69*).

In 1957, Silvette, et al. (*64*) reviewed more than 100 papers concerned with "the immunological aspects of tobacco and smoking." They concluded that inadequate animal studies had been performed in this area. Referring to clinical studies, they observed: "... virtually all reported clinical investigation has been limited to determinations of cutaneous sensitivity to tobacco extracts; and it must be regretfully admitted that much of this published work is equivocal, uncritical, and inadequately controlled."

Such criticism is also applicable to many studies published since then.

Epidemiologic studies designed to determine the prevalence of tobacco allergy have not been carried out; hence, it is difficult to evaluate the magnitude of the problem.

Allergy may be defined as a specific alteration in response mediated by an antigen-antibody reaction. When a hereditary susceptibility to allergic illness is present, the term atopy is used. For example, hay fever and asthma are atopic diseases.

There is no single test or observation which can be used to determine whether a substance may be responsible for allergic disease; however, fulfillment of the following criteria constitutes evidence for such a relationship:

1. Demonstration that the substance is antigenic, i.e., capable of stimulating the production of antibody and then reacting with the antibody.
2. Demonstration that, upon exposure to the substance, signs and symptoms simulating an allergic reaction are elicited which disappear upon its removal.
3. Demonstration that the immunologic event is related to the clinical event.

Recent advances in the understanding of immunological reactions as well as in the methodology of immunology are now being applied

to problems of clinical allergy. For example, Ishizaka (*37*), using radioimmunoelectrophoresis, recently reported that the so-called "allergic antibody" (reagin, skin-sensitizing antibody (SSA), atopic antibody) belongs to a new class of immunoglobulins, IgE.

Although the skin test remains a simple and definitive method of demonstrating reagins in the allergic patient, there are many variables involved in this technique which must be carefully weighed when interpreting test results. In the area of tobacco skin testing, such variables include: differences in antigenic content of the test extract, differences in route of administration, and heterogeneity of test groups.

ANTIGENIC PROPERTIES

Tobacco leaf contains a complex mixture of chemical components including: celluloses, starches, proteins, sugars, alkaloids, pectic substances, hydrocarbons, phenols, fatty acids, isoprenoids, sterols, and inorganic minerals (*69*). Theoretically, relatively few of these substances should be antigenic. Tobacco extracts of different composition result from differences in tobacco types and species, processing of tobacco, and preparation of the extract. Harkavy (*26*) has shown in some patients a differential skin reactivity to extracts from different types of tobacco. Coltoiu, et al. (*9*) reported that 13 different antigens capable of inducing precipitins in rabbits have been isolated from tobacco pollen. Chu, et al. (*7*) prepared aqueous extracts of five commercial tobacco products which stimulated antibody formation in rabbits. The antigens contained in the extracts included both proteins and polysaccharides and had molecular weights ranging from 20,000 to 60,000.

Silvette, et al. (*64*) reviewed several papers dealing with the immunology of nicotine and concluded that nicotine was nonantigenic. Harkavy (*25*), who performed some of the earliest studies on the antigenicity of nicotine, could not exclude the possibility that nicotine may act as a hapten. A hapten is a compound which, although not antigenic by itself, reacts with antibody and conveys antigenic specificity when combined with another compound.

With pyrolysis many of the tobacco constituents undergo reactions involving oxidation, dehydrogenation, cracking, rearrangement, and condensation (*69*). Many new compounds are formed. Pipes (*51*) demonstrated, through exhaustion of passive transfer reactivity in skin sites, that allergy to tobacco smoke in man is distinct from that of allergy to tobacco leaf. Tobacco smoke exhausted reactivity in sites injected with tobacco smoke sensitized serum; reactivity was reduced but not exhausted with tobacco extract. The converse was true with passive transfer sites of tobacco-sensitized serum; tobacco extracts abolished allergic reactivity whereas to-

bacco smoke extract produced a diminution but not total exhaustion. He concluded that it would be useful to test human subjects for both tobacco leaf and tobacco smoke sensitivity. Kreis, et al. (*39*) have speculated that tobacco leaf antigenicity may be lost with pyrolysis.

Coltoiu, et al. (*9*) recently emphasized the importance of removing all irritants from test extracts. In a clinical setting, allergy to tobacco additives such as menthol has also been suspected (*47*).

SKIN TESTING

Intracutaneous injection of test antigen is a widely used method of skin testing. Patch tests have also been used in cases of suspected contact dermatitis.

Rosen (*54*) has observed that skin testing does not accurately duplicate the most common route of exposure to tobacco, i.e., tobacco smoke inhalation. For those involved in the production of tobacco products, inhalation of tobacco dust or direct contact with tobacco may play important roles in sensitization (*9*).

The extensive literature on cutaneous sensitivity to tobacco extracts includes comparisons of the prevalence of positive skin reactions in different groups, such as "normal" nonsmoking adults (*17, 68*), "normal" smokers (*17, 33*), allergic patients (*59, 76*), children (*41, 50*), tobacco workers (*6, 9*), and patients with specific diseases, e.g., thromboangiitis obliterans (*28, 73*). Harkavy reported on tobacco skin reactions in several different groups of patients (*30*). Many of the apparently discordant results in some of these reports can be traced to failure to compare similar populations or to control for differences in the test antigen or in the method of testing.

Sulzberger (*66*) studied the different types of skin reactions produced by intracutaneous injection of denicotinized tobacco extract. Three types of positive skin responses were observed: eczematous reactions; immediate wheal-and-flare reactions; and late reactions, probably of the tuberculin type. The wheal-and-flare response has been by far the predominant type (*42*).

This immediate wheal-and-flare response is a specific immune reaction (*64*) largely mediated by IgE. Patterson (*48*) recently proposed a simplified model explaining the mechanism of action of the skin sensitizing antibody (SSA). "Subsequent to stimulation of the animal by antigen, SSA are produced by cells of the lymphoid system possibly located in the alimentary and respiratory tract.... The SSA so produced are secreted in such a way that they reach the circulation, where circulating cells, predominantly basophilic leukocytes, are sensitized by attachment of the SSA to the cell surface. In addition, the SSA also leave the vascular compartment and sensitize mediator-releasing cells in tissues. The tissue cells are primarily mast cells... The immediate-type allergic reaction occurs

when antigen is introduced into the individual sensitized by SSA, either by transfer of antigenic molecules through the respiratory or alimentary mucosal surface or by injection into the skin or vascular system. The antigens reach the antibody on the surface of the mast cells and initiate the intracellular events that result in mediator release from the cells." The actions of these mediators include smooth muscle contraction, vasodilation, and increased capillary permeability which can produce such clinical pictures as hay fever, asthma, and generalized anaphylaxis.

Until recently, direct skin testing and the passive transfer test (Prausnitz-Küstner reaction) were the only methods of studying IgE mediated responses. In the passive transfer test, serum from an allergic patient is injected into the skin of a normal subject. After a suitable interval the antigen is injected into the prepared site and adjacent normal skin. In a positive response, cutaneous reactivity is transferred to the normal subject at the injection site. The absence of a positive response in nearby normal skin excludes nonspecific irritation as a cause of the response and shows that the normal subject is not himself allergic to the antigen.

Harkavy and Witebsky (*34*) found and selectively absorbed tobacco reagins in patients showing multiple sensitivities. This selective absorption documented the immunologic mechanism of the skin reaction. Passive transfer of the SSA was also reported by Peshkin and Landay (*50*) and by Lima and Rocha (*41*). Lowell (*43*) stated, "The individual possessing skin-sensitizing antibody to the tobacco extract may be regarded as unequivocally allergic to the extract...." Despite the inability of Sulzberger and Feit (*67*) to demonstrate tobacco reagins in their skin test positive patients, several investigators have found them (*26, 50, 75*).

Harkavy (*23*) biopsied urticarial wheals after intradermal injection of tobacco extract and found a local eosinophilia. He felt that this helped confirm the allergic mechanism of the positive skin test. He also biopsied the site of a delayed skin reaction to tobacco and found an eczematous type of response.

The delayed type hypersensitivity reaction is manifested by induration and erythema developing within 24 to 48 hours after injection of antigen. The absence of response in the first 6 to 8 hours after exposure to antigen helps exclude an Arthus reaction, which is also a slowly evolving allergic response. Serum antibodies are not involved in the initiation of delayed type hypersensitivity; rather, the initial step is thought to involve interaction of antigen and specialized lymphocytes (*10, 11*). Contact dermatitis is thought to be very nearly a pure type, delayed hypersensitivity reaction (*10, 11*).

The foregoing discussion has highlighted the studies concerning cutaneous sensitivity to tobacco extracts. Despite the complexities and contradictions, numerous workers agree that tobacco extract

(leaf or smoke) is antigenic and can sensitize (*2, 7, 9, 18, 26, 43, 50, 52, 64, 66, 76*). Silvette, et al. (*64*) concluded, "It is, indeed, beyond question that allergy to tobacco extracts, presumably atopic in nature, is an established fact. . . ."

Lowell (*43*) observed that, in most instances, skin reactivity to an extract of tobacco actually means the presence of allergy in some degree to something in the extract. Armen and Cohen (*2*), Harkavy and Perlman (*31*), and Popescu, et al. (*52*) observed that tobacco extract is weakly antigenic. Armen and Cohen (*2*) were able to sensitize rabbits to tobacco proteins only after absorbing the protein to aluminum hydroxide, which served as an adjuvant.

Even though a positive skin test to tobacco extract may be due to a specific allergic reaction, the interpretation of such a positive test in a given patient or group of patients poses problems, since sensitivity to a battery of antigens has been demonstrated in individuals who are entirely free from allergic symptoms upon exposure to the antigens. Rosen (*54*) stated that this lack of correlation between positive skin tests and clinical symptoms is greater for tobacco than for other antigens such as pollens, dusts, and feathers. He and others have emphasized that the skin test has value only when correlated with clinical evidence.

Analysis of skin test studies in nonsmokers (*64*) shows that approximately 15 percent of such "healthy" individuals give positive reactions to tobacco extracts. Some studies of smokers reporting a 30 percent or more prevalence of skin sensitivity to tobacco extract (*33, 43*) have considered patients with multiple sensitivities, including that to tobacco. Atopic individuals have been noted to have a greater prevalence of skin sensitivity to tobacco than nonatopics (*64*); hence, in some studies an excess of atopic patients may account for a substantial part of the elevated prevalence of tobacco skin sensitivity reported for smokers.

Several workers have sought to use the skin test as a screening device for indicating an unusual susceptibility to the adverse effects of tobacco. DeCrinis, et al. (*13*), Fontana (*17*), and Redisch (*53*) have reported that patients with positive skin tests to tobacco extracts were more likely to have an adverse vascular response to tobacco as indicated by a fall in peripheral skin temperature on smoking. More recent studies have shown that a decrease in skin temperature with smoking is a reproducible response to nicotine found in "normal" individuals and does not appear to be confined to a specific group of smokers (*1, 56, 70*).

ADDITIONAL IMMUNOLOGICAL EFFECTS

Additional evidence is available to support the view that tobacco induces immunologic changes in man and animals. Armen and

Cohen (*2*), Chu, et al. (*7*), Harkavy and Perlman (*31*), and Zussman (*76*) induced precipitin formation in animals sensitized to tobacco extract. Kreis, et al. (*39*) studied precipitation reactions in 651 hospitalized patients, many of whom were suffering from tuberculosis or lung cancer. A precipitation reaction between the patients' sera and a commercial tobacco extract was found in 62.5 percent of the patients. Chu, et al. (*7*), using the same antigens as those employed to stimulate precipitin formation in rabbits, found serum antibodies in 40 percent of a group of smokers which precipitated specificially with the tobacco antigens. Only 7 percent of a group of nonsmokers demonstrated these antibodies.

Savel (*59*) studied eight nonsmoking, allergic individuals who developed immediate upper respiratory discomfort after being exposed to cigarette smoke. As measured by the uptake of tritiated thymidine, the lymphocytes of these individuals were stimulated by cigarette smoke, while "normal" lymphocytes were depressed. The author stated that the correlation of this test with specific forms of clinical allergy remains uncertain.

Some investigators have observed abnormal laboratory test results in smokers as compared to nonsmokers, which may indicate an allergic response in the former group. Schoen and Pizer (*60*) described a smoking woman who demonstrated a striking blood eosinophilia while smoking cigarettes. Upon cessation of smoking, the eosinophil count returned promptly to normal levels. Resumption of smoking was associated with a return of the eosinophilia. Heiskell, et al. (*36*) found a significant increase in C-reactive protein and an abnormal seroflocculant for ethyl choledienate in smokers as compared to nonsmokers. Plasma histaminase levels were reported by Kameswaran, et al. (*38*) to be elevated in smokers.

Experimental animal sensitization to tobacco was reported by Friedlander, et al. (*19*) in male rats. Harkavy (*29*) confirmed these results in male rats and also obtained positive Schultz-Dale reactions in the sensitized animals; however, female rats failed to demonstrate this sensitization. Harkavy (*24*) reported cardiac histological abnormalities in three rabbits sensitized with denicotinized tobacco extracts. The abnormalities found in the three rabbits, respectively, included: intimal proliferation, focal fragmentation of the internal elastic membrane, and loss of smooth muscle fibers in the media of a branch of a coronary artery; focal intimal proliferation and fibrinoid alterations in the media of a small coronary vessel; and a focus of myocardial fibrosis and necrosis.

EFFECT ON THE IMMUNE RESPONSE

The effect of tobacco on the immune response has received some attention. Early studies in rabbits suggested that tobacco smoke re-

tarded the production of agglutinins in rabbits immunized against typhoid (*14*).

A variety of observations indicate that ingestion of antigenic material by the macrophage may be an essential step in the immune response (*3*). Bruni (*5*) found that cigarette smoke suppressed phagocytosis in rabbits. Green and Carolin (*20*) performed *in vitro* studies in rabbit alveolar macrophages and observed that cigarette smoke inhibited the capacity of these cells to inactivate bacteria. Harris, et al. (*35*) reported no differences in the phagocytic ability of macrophages taken from human smokers and nonsmokers, but he also concluded that his data neither contradicted nor supported Green's work. Cohen and Cline (*8*), while noting that macrophages from smokers had normal phagocytic capacity, demonstrated suboptimal macrophage function in an environment of low O_2 tension, a state found more frequently in smokers than nonsmokers. Maxwell, et al. (*45*), using guinea pigs, found that smoke exerted no effect on phagocytosis; nevertheless, smoke seemed to impair the phagocytes' ability to inactivate bacteria. Nicotine has been shown by Meyer, et al. (*46*) to exert a depressant effect on sheep pulmonary alveolar macrophage respiration and ATPase activity. Recently, Yeager (*74*) reported that water soluble constituents of cigarette smoke depress protein-synthesis in rabbit alveolar macrophages *in vitro*.

Lewis, et al. (*40*) found that cigarette smoking had a suppressive action on secretory IgA production in normal subjects but not in subjects with chronic respiratory disorders. Vos-Brat and Rumke (*71*) recently reported that IgG serum concentrations and the response of lymphocytes to phytohemagglutinin were significantly lower in smokers than nonsmokers.

A number of investigators have reported increased rates of respiratory illnesses among cigarette smokers (*70*). Finklea, et al. (*16*) studied antibody response in 289 volunteers after the 1968 Hong Kong influenza epidemic. They reported a significant decrease among cigarette smokers in the persistence of hemagglutination inhibition antibody after natural infection or vaccination with A_2 antigens. They postulated that this antibody deficit among cigarette smokers might be related to increased illness during influenza outbreaks.

IRRITANT AND PHARMACOLOGIC EFFECTS

As Lowell (*43*) has emphasized, the pharmacologic, irritant, and allergic effects of tobacco are difficult to distinguish. Acrolein and acetaldehyde are potent irritants found in tobacco smoke, which, as demonstrated in animal studies, are capable of releasing chemical mediators such as histamine (*58*). The inhalation of tobacco smoke

causes bronchial constriction, mucus hypersecretion, and ciliary stasis (*57*) in man, all of which can contribute to a clinical picture indistinguishable from an allergic reaction. Several authors (*44, 61, 63*) share Sherman's (*62*) view that "... tobacco smoke is an important secondary factor in precipitating allergic symptoms through its action as a nonspecific irritant."

Speer (*65*) recently compared the subjective responses of two groups of nonsmokers to tobacco smoke exposure. One group of 191 patients suffered from documented allergies. In one-sixth of these patients a positive skin test to tobacco extract was found, but only a few patients were seen with objective symptoms which could be traced to tobacco smoke. The other group of 250 patients had no history of allergy and was studied by questionnaire only. Eye irritation, nasal symptoms, headache, and cough were common in both groups. Speer concluded that these effects of tobacco smoke were irritative rather than allergic in origin. The data presented in this study demonstrate that tobacco smoke can contribute to the discomfort of many individuals; they do not rule out a possible contribution from allergic reactions.

Harkavy (*30*) cited experimental data distinguishing allergic effects from pharmacologic effects of smoking such as increased heart rate and decreased skin temperature.

Additional studies are needed to separate the pharmacologic, irritant, and allergic effects of tobacco smoke.

CLINICAL ALLERGY

It is important to understand what role tobacco and tobacco smoke may play in clinical allergy because many individuals are exposed to them in varying concentrations throughout the year.

A variety of conditions have been ascribed to allergic manifestations toward tobacco leaf or smoke including: asthma, rhinitis, urticaria, angioneurotic edema (giant hives), contact dermatitis, migraine headache, gastrointestinal symptoms, and various cardiovascular disturbances (*64*); however, some case reports are lacking in documentation (*4, 49*). A small group of patients having cutaneous sensitivity to tobacco and showing complete disappearance of symptoms when free from exposure to tobacco were reported by Rosen and Levy (*55*). Included in this group were cases of asthma and urticaria.

Studies of atopic individuals have revealed a group of nonsmoking patients with cutaneous sensitivity to tobacco who developed clinical symptoms upon exposure to tobacco smoke (*59, 76*). In none of these studies (*54, 59, 76*) have detailed immunologic investigations, attempting to link clinical and immunologic events, been performed.

Lowell (*43*) reviewed case reports of contact dermatitis to to-

bacco among tobacco workers and noted that because of "...the small proportion of exposed individuals who develop such lesions, and the tendency for it to clear completely when contact with tobacco is avoided and to return on reexposure, an allergic cause in certain instances would appear to be highly probable." Recently, case reports have appeared identifying tobacco smoke and tobacco smoke residue as causes of contact dermatitis (*6, 12, 72*).

Harkavy's (*28*) early reports of a greater number of reactors to tobacco extract among patients with thromboangiitis obliterans (TAO) than among controls drew attention to the cardiovascular system as a possible "susceptible" organ for allergic reactions (*15*). Harkavy continues to be a strong proponent of the role of tobacco allergy in a wide range of cardiovascular abnormalities, including coronary artery disease (*21, 22, 25, 27, 31, 32*). This view on tobacco allergy as one of the etiological factors in coronary heart disease (CHD) has not received much attention.

Silvette, et al. (*64*) reviewed reports (*28, 33, 66, 68, 73*) on the prevalence of skin sensitivity in patients with TAO as compared to controls and cited possible reasons for a higher prevalence of positive skin tests to tobacco in these patients.

In general, the evidence relating TAO to tobacco allergy is inconclusive.

SUMMARY

1. Tobacco leaf, tobacco pollen, and tobacco smoke are antigenic in man and animals.
2. (a) Skin sensitizing antibodies specific for tobacco antigens have been found frequently in smokers and nonsmokers. They appear to occur more often in allergic individuals. Precipitating antibodies specific for tobacco antigens have also been found in both smokers and nonsmokers.
   (b) A delayed type of hypersensitivity to tobacco has been demonstrated in man.
   (c) Tobacco may exert an adverse effect on protective mechanisms of the immune system in man and animals.
3. (a) Tobacco smoke can contribute to the discomfort of many individuals. It exerts complex pharmacologic, irritative, and allergic effects, the clinical manifestations of which may be indistinguishable from one another.
   (b) Exposure to tobacco smoke may produce exacerbation of allergic symptoms in nonsmokers who are suffering from allergies of diverse causes.
4. Little is known about the pathogenesis of tobacco allergy and its possible relationship to other smoking-related diseases.

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Chapter 9

Tobacco Amblyopia

Source: 1971 Report, Chapter 7, pages 431 - 438.

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Tobacco Amblyopia

Tobacco amblyopia (tobacco-alcohol amblyopia) is that syndrome of visual failure occurring in association with the use of tobacco, with or without the concurrent use of alcohol, and with or without concurrent nutritional deficits. The disease has a subacute onset, leading to a loss of visual acuity and color perception (*12*). It is characterized by centrocecal scotomas which are bilateral but not necessarily symmetrical and which have sloping diffuse edges and by the presence of nuclei of denser visual loss within the large scotomas (*22, 23*). Such visual impairment is not unique to tobacco amblyopia, as it is also seen in neurodegenerative disorders, such as Leber's hereditary optic atrophy (*7, 25*).

Clinical information on tobacco amblyopia has appeared in numerous articles throughout the past century. This information has been reviewed by Silvette, et al. (*17*) and, more recently, by Dunphy (*5*). Pure tobacco amblyopia (TA), that is amblyopia unassociated with excessive alcohol intake or the exposure to other toxins, is rarely seen in the United States today (*12*). Walsh, et al. (*23*) have observed that when TA is found it is usually present in association with nutritional or idiopathic vitamin deficiencies. Victor (*22*) recently observed that the type of visual defect seen in tobacco amblyopia may be found in clinical circumstances in which tobacco is clearly not a causative factor. He questions whether TA is distinguishable from other forms of amblyopia.

The prevalence of this disorder has been variously estimated in the past at from 0.5 to 1.5 percent of all eye clinic patients (*20, 23*). However, currently in the United States, it appears to be a rare condition. Silvette, et al. (*17*) have observed that the incidence of tobacco amblyopia appears to have decreased substantially during the past decades. Other authors (*3, 15*) have also commented on this trend. Although reference has been made to the increased frequency of certain types of tobacco usage in patients with this disorder, adequate population studies with proper controls have yet to be performed. The association of this disorder with the use of tobacco is strengthened by the frequent clinical observations of improvement following the cessation of smoking although improvement has been noted by some to occur without cessation.

Research into the pathogenesis of tobacco amblyopia has cen-

tered upon the interrelationships of cyanide metabolism, vitamin B_{12}, and other vitamin deficiencies. Three reviews of this material have recently appeared (*1*, *12*, *22*). Numerous studies reviewed in these articles suggest that tobacco amblyopia may result from the incomplete detoxification of the cyanide present in tobacco smoke. This failure of detoxification may stem from or be intensified by inadequate dietary intake of necessary nutritional factors. This may be the reason for the association of this disorder with excessive alcohol intake and with its related nutritional deficits (*2*, *4*, *6*, *8*, *9*, *10*, *11*, *13*, *14*, *16*, *18*, *19*, *21*, *24*, *26*, *27*, *28*).

SUMMARY AND CONCLUSIONS

Tobacco amblyopia is presently a rare disorder in the United States. The evidence suggests that this disorder is related to nutritional or idiopathic deficiencies in certain detoxification mechanisms, particularly in handling the cyanide component of tobacco smoke.

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Chapter 10

Pipes and Cigars

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Introduction

This chapter is a review of the epidemiological, pathological, and experimental data on the health consequences of smoking cigars and pipes, alone, together, and in various combinations with cigarettes. Previous reviews on the health consequences of smoking have dealt primarily with cigarette smoking. Although some of the material on pipes and cigars presented in this chapter has been presented in previous reports of the Surgeon General, this is the first attempt to summarize what is known about the health effects of pipe and cigar smoking. Since the use of pipes and cigars is limited almost exclusively to men in the United States, only data on men are included in this review.

The influence of pipe and cigar smoking on health is determined by examining the overall and specific mortality and morbidity experienced by users of these forms of tobacco compared to nonsmokers. Epidemilogical evidence suggests that individuals who limit their smoking to only pipes or cigars have overall mortality rates that are slightly higher than nonsmokers. For certain specific causes of death, however, pipe and cigar smokers experience mortality rates that are as great as or exceed those experienced by cigarette smokers. This analysis becomes more complex when combinations of smoking forms are examined. The overall mortality rates of those who smoke pipes, cigars, or both in combination with cigarettes appear to be intermediate between the high mortality rates of cigarette smokers and the lower rates of those who smoke only pipes or cigars. This might seem to suggest that smoking pipes or cigars in combination with cigarettes diminishes the harmful effects of cigarette smoking. However, an analysis of mortality associated with smoking combinations of cigarettes, pipes, and cigars should be standardized for the level of consumption of each of the products smoked in terms of the amount smoked, duration of smoking, and the depth and degree of inhalation. For example, cigar smokers who also smoke a pack of cigarettes a day might be expected to have mortality rates somewhat higher than those who smoke only cigarettes at the level of a pack a day, assuming that both groups smoke their cigarettes in the same way. Mixed smokers who inhale pipe or cigar smoke in a manner similar to the way they smoke cigarettes might be expected to have higher mortality rates than mixed smokers who do not inhale their cigars and pipes and also

resist inhaling their cigarettes. Unfortunately, little of the published material on mixed cigarette, pipe, and cigar smoking contains these types of analyses or controls.

A paradox seems to exist between the mortality rates of ex-smokers of pipes and cigars and ex-smokers of cigarettes. Ex-cigarette smokers experience a relative decline in overall and certain specific causes of mortality following cessation. This decline is important but indirect evidence that cigarette smoking is a major cause of the elevated mortality rates experienced by current cigarette smokers. In contrast to this finding, several prospective epidemiological investigations, Hammond and Horn (*40*), Best (*9*), Kahn (*50*), and Hammond (*38*), have reported higher death rates for ex-pipe and ex-cigar smokers than for current pipe and cigar smokers. This phenomenon was analyzed by Hammond and Garfinkel (*39*). The development of ill health often results in a cigarette smoker giving up the habit, reducing his daily tobacco consumption, switching to pipes or cigars, or choosing a cigarette low in tar and nicotine. In many instances, a smoking-related disease is the cause of ill health. Thus, the group of ex-smokers includes some people who are ill from smoking-related diseases, and death rates are high among persons in ill health.

As a result, ex-cigarette smokers initially have higher overall and specific mortality rates than continuing cigarette smokers, but because of the relative decrease in mortality that occurs in those who quit smoking for reasons other than ill health, and because of the dwindling number of ill ex-smokers, a relative decrease in mortality is observed (within a few years) following cessation of cigarette smoking. The beneficial effects of cessation would be obvious sooner were it not for the high mortality rates of those who quit smoking for reasons of illness. A similar principle operates for ex-pipe and ex-cigar smokers, but because of the lower initial risk of smoking these forms and therefore the smaller margin of benefit following cessation, the effect produced by the ill ex-smokers creates a larger and more persistent impact on the mortality rates than is seen in cigarette smoking.

For the above reasons a bias is introduced into the mortality rates of current smokers and ex-smokers of pipes and cigars, so that a more accurate picture of mortality might be obtained by combining the ex-smokers with the current smokers and looking at the resultant mortality experience.

Because of a lack of data that would allow a precise analysis of mortality among ex-pipe and ex-cigar smokers, a detailed analysis of these groups could not be undertaken in this review.

For each specific cause of death, tables have been prepared which summarize the mortality and relative risk ratios reported in the major

prospective and retrospective studies which contained information about pipe and cigar smokers. The smoking categories used include: cigar only, pipe only, total pipe and cigar, cigarette only, and mixed. The total pipe and cigar category includes: those who smoke pipes only, cigars only, and pipes and cigars. The mixed category includes: those who smoke cigarettes and cigars; cigarettes and pipes; and cigarettes, pipes, and cigars. Mortality and relative risk ratios were calculated relative to nonsmokers.

The Prevalence of Pipe, Cigar, and Cigarette Usage

The prevalence of pipe, cigar, and cigarette smoking in the United States was estimated by the National Clearinghouse for Smoking and Health from population surveys conducted in 1964, 1966, and 1970 (*98*, *99*, *100*). In each survey, about 2,500 interviews were conducted on a national probability sample stratified by type of population and geographic area. The use of these products among adults aged 21 and older is summarized in tables 1 and 2. The prevalence of pipe, cigar, and cigarette smoking in Great Britain for the years 1965, 1968, and 1971 is presented in table 3.

TABLE 1.—*Percent distribution of U.S. male smokers aged 21 and older by type of tobacco used for the years 1964, 1966, and 1970*

Forms used	1964 (percent)	1966 (percent)	1970 (percent)
1. Cigar only	6.8	5.5	5.6
2. Pipe only	1.7	3.0	3.6
3. Pipe and cigar	3.9	4.9	4.4
4. Cigarette only	28.6	31.2	25.9
5. Cigarette and cigar	11.3	9.9	6.6
6. Cigarette and pipe	5.3	4.9	5.3
7. Cigarette, pipe, and cigar	7.7	6.3	4.6
8. Nonsmoker	34.7	34.3	44.0
Total	100.0	100.0	100.0
Number of persons in sample	2,389	2,679	2,861
Total pipe users (2+3+6+7)	18.7	19.2	17.9
Total cigar users (1+3+5+7)	29.9	26.7	21.2
Total cigarette users (4+5+6+7)	52.9	52.4	42.3

Source: U.S. Department of Health, Education, and Welfare (*98*, *99*, *100*).

TABLE 2.—*Percent distribution of U.S. male smokers by type of tobacco used and age for 1970*

Forms used	Age groups				
	21 to 34	35 to 44	45 to 54	55 to 64	65 to 75 +
1. Cigar only	3. 7	6. 5	4. 7	6. 7	9. 3
2. Pipe only	4. 3	3. 5	3. 0	3. 2	3. 6
3. Pipe and cigar	3. 8	3. 3	5. 2	4. 4	6. 9
4. Cigarette only	28. 8	29. 0	27. 1	24. 3	13. 6
5. Cigarette and cigar	6. 8	10. 4	5. 5	5. 2	4. 2
6. Cigarette and pipe	6. 6	4. 4	5. 6	4. 0	3. 8
7. Cigarette, pipe, and cigar	5. 8	4. 8	5. 0	4. 0	1. 4
8. Nonsmoker	40. 2	38. 1	43. 9	48. 2	57. 2
Total	100. 0	100. 0	100. 0	100. 0	100. 0
Number of persons in sample	1, 009	528	523	405	388
Total pipe users	20. 5	16. 0	18. 8	15. 6	15. 7
Total cigar users	20. 1	25. 0	20. 4	20. 3	21. 8
Total cigarette users	48. 1	48. 6	43. 3	37. 5	23. 0

Source: U.S. Department of Health, Education, and Welfare (*100*).

TABLE 3.—*Percent distribution of British male smokers aged 25 and older by type of tobacco used for the years 1965, 1968, and 1971*

Forms used	1965	1968	1971
1. Cigars only	1. 9	2. 8	3. 3
2. Pipe only	5. 1	5. 6	5. 9
3. Cigarettes only	46. 8	45. 7	40. 8
4. Cigarettes and pipe	8. 0	7. 0	6. 1
5. Mixed smokers	7. 5	9. 1	8. 4
6. Nonsmokers	30. 7	29. 9	35. 4
Total	100. 0	100. 0	100. 0
Number of persons in sample	3, 576	3, 566	3, 594
Total pipe users	13. 9	14. 3	13. 3
Total cigar	9. 0	11. 7	11. 3
Total cigarette	67. 6	67. 6	61. 6

Source: Todd, G. F. (*94*).

The Definition and Processing of Cigars, Cigarettes, and Pipe Tobaccos

Cigarettes

The U.S. Government has defined tobacco products for tax purposes. Cigarettes are defined as "(1) Any roll of tobacco wrapped in paper or in any substance not containing tobacco, and (2) any roll of tobacco wrapped in any substance containing tobacco which, because of its appearance, the type of tobacco used in the filler, or its packaging and labeling, is likely to be offered to, or purchased by, consumers as a cigarette described in subparagraph (1)." Cigarettes are further classified by size, but virtually all cigarettes sold in the United States are "small cigarettes" which by definition weigh "not more than 3 pounds per thousand" which is not more than 1.361 grams per cigarette (*96*).

American brands of cigarettes contain blends of different grades of Virginia, Burley, Maryland, and oriental tobaccos. Several varieties of cigarette tobaccos are flue-cured. In this process, tobacco leaves are cured in closed barns where the temperature is progressively raised over a period of several days. This results in "color setting," fixing, and drying of the leaf. The most conspicuous change is the conversion of starch into simpler sugars and suppression of oxidative reactions. Flue-cured tobaccos produce an acidic smoke of light aroma (*35*, *112*).

Cigars

Cigars have been defined for tax purposes as: "Any roll of tobacco wrapped in leaf tobacco or in any substance containing tobacco (other than any roll of tobacco which is a cigarette within the meaning of subparagraph (2) of the definition for cigarette)" (*112*). In order to clarify the meaning of "substance containing tobacco" the Treasury department has stated that, "The wrapper must (1) contain a significant proportion of natural tobacco; (2) be within the range of colors normally found in natural leaf tobacco; (3) have some of the other characteristics of the tobaccos from which produced; e.g., nicotine content, pH, taste, and aroma; and (4) not be so changed in the reconstitution process that it loses all the tobacco characteristics" (*102*). Further, "To be a cigar, the filler must be substantially of tobaccos unlike those in ordinary cigarettes and must not have any added flavoring which would cause the product to have the taste or aroma generally attributed to cigarettes. The fact that a product does

not resemble a cigarette (such as many large cigars do not) and has a distinctive cigar taste and aroma is of considerable significance in making this determination" (*102*).

Cigars are also classified by size. "Small cigars" weigh not more than 3 pounds per thousand and "large cigars" weigh more than 3 pounds per thousand. "Large cigars" are further divided into seven classes for tax purposes based on the retail price intended by the manufacturer for such cigars (*96*).

Cigars are made of filler, binder, and wrapper tobaccos. Most cigar tobaccos are air-cured and then fermented. More recently, reconstituted cigar tobaccos have been used as wrapper, binder, or both. Cigars are either hand-rolled or machine made. Some brands of small cigars are manufactured on regular cigarette making machines. The aging and fermentation processes used in cigar tobacco production produce chemical catalytic, enzymatic, or bacterial transformations as evidenced by increased temperature, oxygen utilization, and carbon dioxide generation within fermenting cigar tobaccos. In this complex process, up to 20 percent of the dry weight of the leaf is lost through decreases in the concentration of the most readily fermentable materials such as carbohydrates, proteins, and alkaloids. The flavor and aroma of cigar tobaccos are in large measure the results of precisely controlled treatment during the fermentation process (*35*, *36*, *112*).

Pipe Tobaccos

The definition of pipe tobacco used by the U.S. Government was repealed in 1966 and there is no Federal tax on pipe tobaccos. The most popular pipe tobaccos are made of Burley; however, many pipe tobaccos are blends of different types of tobacco. A few contain a significant proportion of midrib parts that are crushed between rollers. "Saucing" material, or casings containing licorice, sweetening agents, sugars, and other flavoring materials are added to improve the flavor, aroma, and smoke taste. These additives modify the characteristics of smoke components (*112*).

Conclusion

Because of the unique curing and processing methods used in the production of cigar and pipe tobaccos, significant physical and chemical differences exist between pipe and cigar tobaccos and those used in

cigarettes. The extent to which these changes may alter the health consequences of smoking pipes and cigars can best be estimated by an analysis of the potentially harmful chemical constitutents found in the smoke of these tobaccos, the tumorigenic activity of smoke condensates in experimental animals, and a review of the epidemiological data which has accumulated on the health effects of pipe and cigar smoking.

Chemical Analysis of Cigar Smoke

Only a few studies have been conducted that compare the chemical constituents of cigar smoke with those found in cigarette smoke. Hoffmann, et al. (*43*) compared the yields of several chemical components in the smoke from a plain 85 mm. cigarette, two types of cigars, and a pipe. The particulate matter, nicotine, benzo(a)pyrene, and phenols were determined quantitatively in the smoke of these tobacco products. One cigar tested was a 135-mm.-long, 7.8-g., U.S.-made cigar. The other was a handmade Havana cigar 147 mm. long weighing 8.6 g. The relative content of nicotine in the particulate matter produced by the cigars was similar to that of the cigarette tars. The benzo(a)pyrene and phenol concentrations in the cigar condensate was two to three times greater than in cigarette "tar" (table 4). Kuhn (*58*) compared the alkaloid and phenol content in condensates from an 80-mm. Bright-blend cigarette sold commercially in Austria with that obtained from 103-mm. cigars. These were tested

TABLE 4.—*Amounts of several components of 1 g. of particulate material from mainstream smoke of tobacco products*

Compound	Tobacco product [1]					
	U.S. cigar A (b)	Havana cigar B (b)	Standard pipe tobacco in pipe (b)	Cigarette tobacco in pipe	85 mm. plain U.S. cigarette (a)	85 mm. plain U.S. cigarette (b)
Nicotine (mg.)	46. 2	63. 6	56. 1	61. 0	65. 9	77. 4
Benzo(a)pyrene (μg.)	3. 9	3. 6	6. 0	3. 6	1. 2	1. 3
Phenol (mg.)	8. 2	6. 7	15. 0	7. 3	2. 9	4. 1
o-Cresol (mg.)	1. 6	1. 7	1. 9	1. 4	. 6	. 8
m+*p*-Cresol (mg.)	4. 8	3. 8	5. 6	3. 4	1. 4	1. 9
m+*p*-Ethylphenol (mg.)	1. 1	1. 5	1. 1	1. 3	. 7	. 7

[1] Smoking conditions:
(a) 1 puff per minute, duration 2 sec., puff volume 35 ml.
(b) 2 puffs per minute, duration 2 sec., puff volume 35 ml.

Source: Hoffmann, et al. (*43*).

with and without the use of a cellulose acetate filter. The concentrations of total alkaloids and phenol in the cigar smoke condensate were essentially the same as in the cigarette condensate, but pyridine values were about 2½ times higher in the cigar condensate.

Campbell and Lindsey (*17*) measured the polycyclic hydrocarbon levels in the smoke of a small popular-type cigar 8.8 cm. long, weighing 1.9 g. Significant quantities of anthracene, pyrene, fluoranthene, and benzo(a)pyrene were detected in the unsmoked cigar tobacco, in concentrations much greater than those found in Virginia cigarettes but of the same order as those found in some pipe tobaccos. The smoking process contributed considerably to the hydrocarbon content of the smoke. Table 5 compares the concentrations in the mainstream smoke of cigarettes, cigars, and pipes of four hydrocarbons frequently found in condensates. The authors reported that the mainstream smoke from a popular brand of small cigar contained the polycyclic aromatic hydrocarbons; acenaphthylene, phenanthrene, anthracene, pyrene, fluoranthene, and benzo(a)pyrene. The concentrations of these hydrocarbons in the mainstream smoke were greater than those found in Virginia cigarette smoke.

Osman, et al. (*69*) analyzed the volatile phenol content of cigar smoke collected from a 7-g. American-made cigar with domestic filler. After quantitative analysis of phenol, cresols, xylenols, and meta and para ethyl phenol, the authors concluded that the levels of these compounds were generally similar to those reported for cigarette smoke. Osman and Barson (*68*) also analyzed cigar smoke for benzene, toluene, ethyl benzene, m-, p-, and o-xylene, m- and p-ethyltoluene, 1,2,4-trimethylbenzene, and dipentene, and generally found levels within the range of those previously reported for cigarette condensates.

In summary, available evidence suggests that cigar smoke contains many of the same chemical constituents, including nicotine and other alkaloids, phenols, and polycyclic aromatic hydrocarbons as are found

TABLE 5.—*A comparison of several chemical compounds found in the mainstream smoke of cigars, pipes, and cigarettes*

Compound	Micrograms per 100 g. of tobacco consumed		
	Cigars	Pipes [1]	Cigarettes
Acenaphthylene	1. 6	29. 1	5. 0
Anthracene	11. 9	110. 0	10. 9
Pyrene	17. 6	75. 5	12. 5
3,4-benzpyrene	3. 4	8. 5	. 9

[1] This is a light pipe tobacco.

Source: Campbell, J. M., Lindsey, A. J. (*17*).

in cigarette smoke. Most of these compounds are found in concentrations which equal or exceed levels found in cigarette "tar." A more complete picture of the carcinogenic potential of cigar "tars" is obtained from experimental data in animals.

Mortality

Overall Mortality

Several large prospective studies have examined the health consequences of various forms of smoking. The results of these investigations have been reviewed in previous reports of the Surgeon General in which the major emphasis has been on cigarette smoking and its effect on overall and specific mortality and morbidity. The following pages present a current review of the health consequences of smoking pipes and cigars. Data from the prospective investigations of Dunn, et al. (*31*), Buell, et al. (*16*), Hirayama (*42*), and Weir and Dunn (*105*) are not cited, because in these studies a separate category for pipe and cigar smokers was not established.

The smoking habits and mortality experience of 187,783 white men between the ages of 50 and 69 who were followed for 44 months were reported by Hammond and Horn (*41*). The overall mortality rates of men who smoked pipes or cigars were slightly higher than the rates of men who never smoked. The overall mortality rate of cigar smokers was slightly higher than that of pipe smokers.

In a study of 41,000 British physicians, Doll and Hill (*26*, *27*) reported the overall mortality of pipe and cigar smokers as being only 1 percent greater than that among nonsmokers. Best (*9*), in a study of 78,000 Canadian veterans, reported overall mortality rates of pipe and cigar smokers slightly above those of nonsmokers. Kahn (*50*) examined the death rates and smoking habits of more than 293,000 U.S. veterans and Hammond (*38*) examined the smoking habits of and mortality rates experienced by 440,559 men. In these studies, pipe smokers experienced mortality rates similar to those of men who never smoked regularly, whereas cigar smokers had death rates somewhat higher than men who never smoked regularly. Table 6 summarizes the results of these five studies.

Thus, data from the major prospective epidemiological studies demonstrate that the use of pipes and cigars results in a small but definite increase in overall mortality. Cigar smokers have somewhat higher death rates than pipe smokers, and mixed smokers who use cigarettes in addition to pipes and cigars appear to experience an intermediate level of mortality that approaches the mortality experience of cigarette smokers.

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TABLE 6.—*Mortality ratios for total deaths by type of smoking (males only)*

Author, reference	Smoking type							
	Non-smoker	Cigar only	Pipe only	Cigar and pipe	Cigarette and cigar	Cigarette and pipe	Mixed (cigarette and other)	Cigarette only
Hammond and Horn [1] (*40*)	1.00	1.22	1.12	1.10	1.36	1.50	1.43	1.68
Doll and Hill (*26*)	1.00	----	----	1.01	------	-------	1.11	1.28
Best (*9*)	1.00	1.06	1.05	.98	1.22	1.26	1.13	1.54
Kahn (*50*)	1.00	1.10	1.07	1.08	------	-------	1.51	1.84
Hammond [2] (*38*)	1.00	1.25	1.19	1.01	------	-------	1.57	1.86

[1] Only mortality ratios for ages 50 to 69 are presented.
[2] Only mortality ratios for ages 55 to 64 are presented.

Mortality and Dose-Response Relationships

A consistent association exists between overall mortality and the total dose of smoke a cigarette smoker receives. The methods most frequently used to measure dosage of tobacco products are: Amount smoked, degree of inhalation, duration of smoking experience, age at initiation, and the amount of tar in a given tobacco product. For cigarette smokers, the higher the dose as measured by any of these parameters, the greater the mortality. The significance of the small increase in overall mortality that occurs for the entire group of pipe and cigar smokers can be analyzed by examining the mortality of subgroups defined by similar measures of dosage as used in the study of cigarette smokers.

AMOUNT SMOKED

Hammond and Horn (*40*) reported an increase in the overall mortality of pipe and cigar smokers with an increase in the amount smoked. Individuals who smoked more than four cigars a day or more than 10 pipefuls a day had death rates significantly higher than men who never smoked ($P<0.05$ for cigar smokers and $P<0.05$ for pipe smokers) (table 7). Cigar and pipe users who smoked less than this amount experienced an overall mortality similar to men who never

smoked. The study of Canadian veterans (*9*) also contained evidence of a dose-response in mortality by amount smoked for cigar smokers. No dose-response relationship was observed among pipe smokers (table 8). Kahn (*50*) reported a consistent increase in overall mortality with an increase in the amount smoked for both pipe and cigar smokers (table 9). Hammond (*38*) found no consistent relationship between overall mortality and the number of cigars or pipefuls smoked (table 10).

TABLE 7.—*Mortality ratios for total deaths of cigar and pipe smokers by amount smoked—Hammond and Horn*

Amount smoked	Number of deaths		
	Observed	Expected	Mortality ratio
Nonsmoker	1, 664	1, 664	1. 00
Cigar only:			
Total	653	598	1. 09
1 to 4 cigars	410	400	1. 03
>4 cigars	229	185	1. 24
Pipe only:			
Total	609	560	1. 09
1 to 10 pipefuls	391	374	1. 05
>10 pipefuls	204	172	1. 19

Source: Hammond, E. C., Horn, D. (*40*).

TABLE 8.—*Mortality ratios for total deaths of cigar and pipe smokers by amount smoked—Best*

Amount smoked	Number of deaths		
	Observed	Expected	Mortality ratio
Nonsmoker	----------	----------	1. 00
Cigar only:			
Total	90	82. 07	1. 10
1 to 2 cigars	64	56. 05	1. 14
3 to 10 cigars	23	19. 40	1. 19
>10 cigars	1	1. 59	. 63
Pipe only:			
Total	570	566. 99	1. 00
1 to 10 pipefuls	374	370. 09	1. 01
10 to 20 pipefuls	141	140. 84	1. 00
>20 pipefuls	36	35. 90	1. 00

Source: Best, E. W. R. (*9*).

The above evidence suggests that a dose-response relationship may exist between the number of cigars and pipefuls smoked and overall mortality. However, because of the high-mortality rate of ex-smokers of cigars and pipes, it is difficult to interpret the data presented without including this group with the continuing smokers. Without data which examines patterns of both daily rate of smoking and inhalation at various age levels, no firm conclusions can be drawn as to the nature of this dosage relationship.

TABLE 9.—*Mortality ratios for total deaths of cigar and pipe smokers by age and amount smoked—Kahn*

Amount smoked	Mortality ratio, age	
	55 to 64	65 to 74
Nonsmoker	1.00	1.00
Cigar only:		
Total	1.01	1.08
1 to 4 cigars per day	.89	1.00
5 to 8 cigars per day	1.14	1.23
>8 cigars per day	1.65	1.28
Pipe only:		
Total	1.08	1.06
1 to 4 pipefuls per day	1.16	.91
5 to 19 pipefuls per day	1.04	1.10
>19 pipefuls per day	----------	1.18

Source: Kahn, H. A. (60).

TABLE 10.—*Mortality ratios for total deaths of cigar and pipe smokers by amount smoked—Hammond*

Amount smoked	Mortality ratio	Amount smoked	Mortality ratio
Nonsmoker	1.00	Current pipe smokers:	
Current cigar smokers:		Total	1.04
Total	1.09	1 to 9 pipefuls per day	1.08
1 to 4 cigars per day	1.03	>9 pipefuls per day	.92
>4 cigars per day	1.18		

Source: Hammond, E. C. (58).

Inhalation

Inhalation of tobacco smoke directly exposes the bronchi and the lungs to smoke and results in the absorption of the soluble constituents of the gas and particulate phases. Without inhalation tobacco smoke only reaches the oral cavity and the upper digestive and respiratory tracts and does not reach the lungs where further direct effects and systemic absorption of various chemical compounds can occur.

Although the smoker has some voluntary control over the inhalation of smoke, the physical and chemical properties of tobacco smoke to a degree determine its acceptability and "inhalability."

The condensate of pipe and cigar smoke is generally found to be alkaline when the pH is measured by suspending a Cambridge filter in CO_2-free water. Cigarette condensate is slightly acidic as measured by this method. Since alkaline smoke is more irritating to the respiratory tract, it has been assumed that the more alkaline smoke of pipes and cigars was in part responsible for the lower levels of inhalation reported by pipe and cigar smokers. Brunnemann and Hoffmann (*15*) have analyzed the pH of whole, mainstream smoke of cigarettes and cigars on a puff-by-puff basis using a pH electrode suspended in mainstream smoke. Smoke from several U.S. brands of cigarettes was found to be acidic throughout the entire length of the cigarette. Of interest was the finding that cigar smoke also had an acidic pH for the first two-thirds of the cigar and became alkaline only in the last 20 to 40 percent of the puffs from the cigar. Available epidemiological evidence indicates that most cigar smokers do not inhale the smoke and most cigarette smokers do. The fact that smoke from the first half or more of a cigar is acidic, near the range of pH values commonly found in cigarette smoke, and becomes alkaline only toward the end of the cigar might suggest that the pH of the smoke of a tobacco product may not be the only factor that influences inhalation patterns. Perhaps "tar" and nicotine levels as well as the concentration of other "irritating" chemicals also affect the degree to which a tobacco smoke will be inhaled.

Nicotine is rapidly absorbed into the blood stream from the lungs when tobacco smoke is inhaled. The amount of nicotine absorbed from the lungs is primarily a function of the nicotine concentration in the smoke and the depth of inhalation. Some nicotine may also be absorbed through the mucous membranes of the mouth. This is more likely to occur under alkaline conditions when nicotine is unprotonated (*3*, *15*, *79*). This suggests that cigar smokers may be able to absorb some nicotine through the oral cavity without having to inhale, particularly during the time that the smoke from the cigar is alkaline.

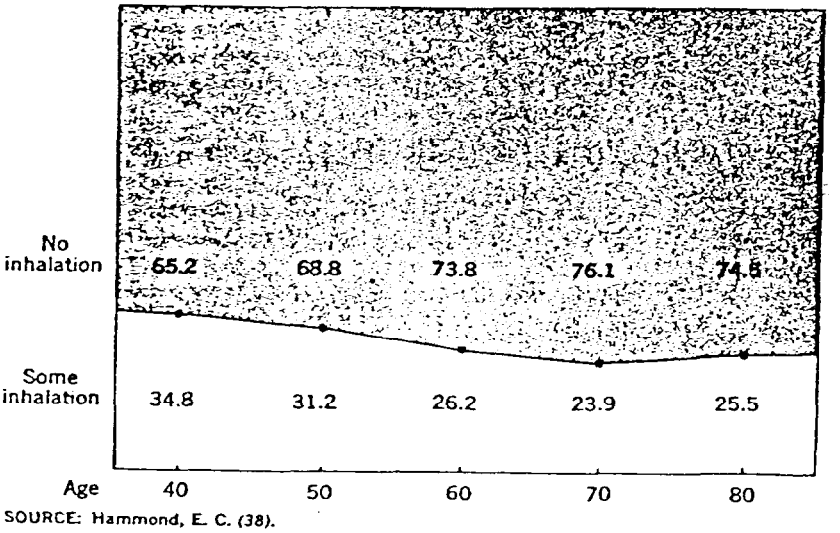
With the development of sensitive measures of serum nicotine levels (*48*) the extent to which nicotine is absorbed through the membranes of the mouth in pipe and cigar smokers can be more accurately determined.

Inhalation patterns of smokers were determined in several of the large prospective and some of the retrospective epidemiological studies. Inhalation was usually determined by the administration of a questionnaire that required a subjective evaluation of one's own patterns of inhalation. Although the accuracy of these questionnaires has not been confirmed by an objective measure of inhalation, such as carboxyhemoglobin or serum nicotine levels, their reliability is supported by mortality data which demonstrate higher overall and specific death rates with self-reported increases in the depth of inhalation.

Doll and Hill (*26*) and Hammond (*38*) presented information on inhalation patterns of pipe, cigar, and cigarette smokers (figs. 1, 2, 3, and table 12). Some 80 to 90 percent of cigarette smokers reported inhaling, with the majority of individuals inhaling moderately or deeply, whereas most pipe and cigar smokers denied inhaling at all. Pipe smokers reported slightly more inhalation than cigar smokers. For each type of smoking, less inhalation was reported by older smokers. This change may represent less awareness of inhalation, differences in smoking habits of successive cohorts of smokers, or it may reflect the operation of selective factors which favor survival of noninhalers.

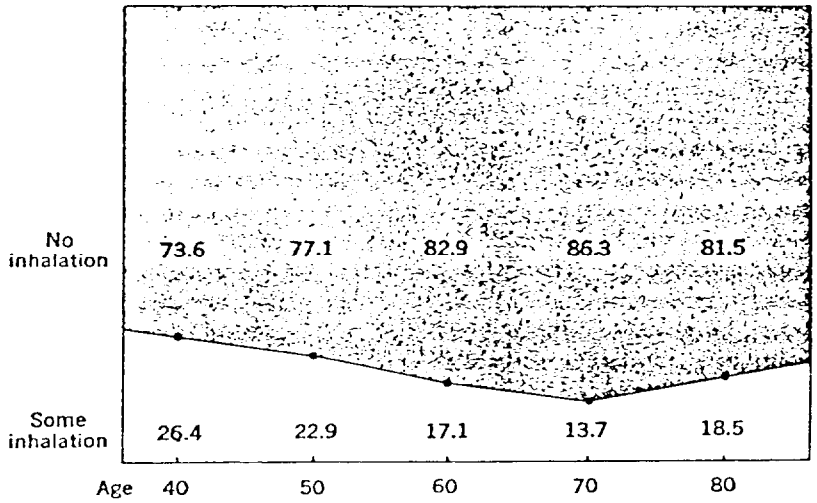
The Tobacco Research Council of the United Kingdom has, since 1957, periodically reported the use of tobacco products by the British.

Figure 1.—Inhalation among pipe smokers by age.



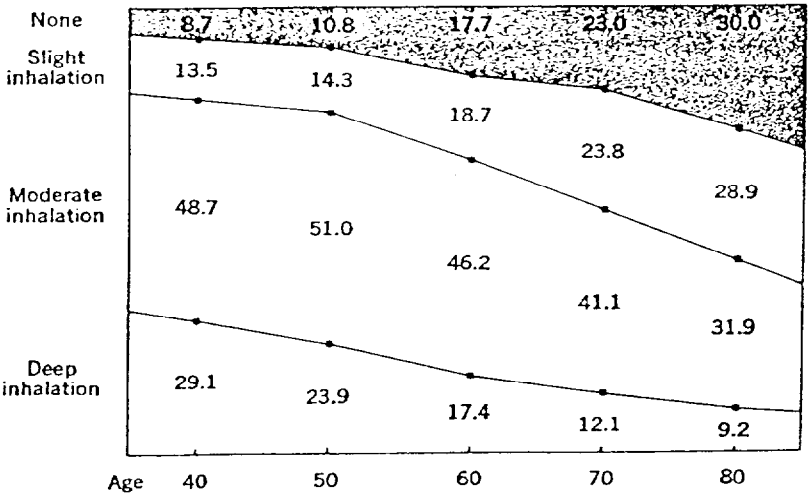
SOURCE: Hammond, E. C. (*38*).

Figure 2.—Inhalation among cigar smokers by age—Hammond.



SOURCE: Hammond, E. C. (38).

Figure 3.—Depth of inhalation among cigarette smokers by age.—Hammond.



SOURCE: Hammond, E. C. (38).

Recent reports edited by Todd have contained data on the inhalation pattern of cigar, pipe, and cigarette smokers (*92*, *93*, *94*). Table 11 shows that most cigarette smokers inhale a "lot" of "fair amount" whereas most pipe and cigar smokers do not inhale at all or "just a little." Little change is observed in the inhalation patterns of a given product since 1968.

Best (*9*) reported inhalation data among male cigarette smokers by smoking intensity and age group, but did not report the inhalation

patterns of pipe and cigar smokers. The overall mortality rates of current pipe smokers who inhaled at least slightly were reported by Hammond (*38*) as being somewhat higher than for men who never smoked regularly. The overall mortality rates of current cigar smokers who reported inhaling at least slightly were appreciably higher than for men who never smoked regularly (table 13).

Available evidence indicates that cigarette smokers inhale smoke to a greater degree than smokers of cigars or pipes. Once a smoker has learned to inhale cigarettes, however, there appears to be a tendency to also inhale the smoke of other tobacco products. For cigars, this is evidently true whether one smokes both cigarettes and cigars or switches from cigarettes to cigars (tables 14, 15, 16).

Bross and Tidings (*14*) examined the inhalation patterns of smokers of large cigars, cigarettes, and those who switched from one tobacco product to another (table 15). Nearly 75 percent of those who were currently smoking only cigarettes reported inhaling "almost every puff" and only 7 percent never inhaled. The opposite was true for persons who had always smoked only cigars among whom 4 percent re-

TABLE 11.—*The extent of inhaling pipes, cigars, and cigarettes by British males aged 16 and over in 1968 and 1971*

Amount of inhalation	Tobacco product					
	Cigars		Pipes		Cigarettes	
	1968	1971	1968	1971	1958	1971
Inhale a lot	23	19	8	8	47	47
Inhale a fair amount	16	19	10	8	31	30
Inhale just a little	27	27	24	26	13	15
Do not inhale at all	34	35	59	58	9	8
Total	100	100	100	100	100	100

Source: Todd, G. F. (*93, 94*).

TABLE 12.—*Inhalation among cigar, pipe, and cigarette smokers by age—Doll and Hill*

Smoking type	Percentage of inhalers, age					
	25 to 34	35 to 44	45 to 54	55 to 64	65 to 74	>74
Cigar and pipe	12.00	10.00	7.00	5.00	4.00	4.00
Mixed (cigarette and other)	74.00	60.00	47.00	36.00	30.00	26.00
Cigarette only	90.00	85.00	75.00	66.00	58.00	41.00

Source: Doll, R., Hill, A. B. (*26*).

ported inhaling almost every puff and 89 percent said they never inhaled. Cigar smokers who also smoked cigarettes reported intermediate levels of inhalation between the cigar only and cigarette only categories. Inhalation patterns were similar whether the individual continued to smoke both products, stopped smoking cigarettes but continued smoking cigars, or stopped smoking cigarettes and switched to cigars. In all three groups, about 20 percent reported inhaling "almost every puff." This suggests that once an individual's inhalation patterns are established on cigarettes, he may be more likely to inhale cigar smoke if he switches to cigars, or uses both cigars and cigarettes, than the cigar smoker who has not smoked cigarettes.

Todd (*93*) reported similar data for a sample of smokers in the United Kingdom (table 16). The prevalence of inhaling a "lot" or "fair amount" of smoke was highest among cigarette smokers who were currently smoking cigarettes (77 percent) and lowest among current cigar smokers who had previously smoked only cigars or pipes (18 percent). Individuals who switched from cigarettes to cigars main-

TABLE 13.—*Mortality ratios for total deaths of cigar and pipe smokers by age and inhalation—Hammond*

Inhalation	Mortality ratio, age	
	45 to 64	65 to 84
Nonsmoker	1.00	1.00
Cigar only:		
Total	1.09	.98
No inhalation	1.02	.91
Some inhalation	1.28	1.37
Pipe only:		
Total	1.04	.95
No inhalation	.98	.87
Some inhalation	1.21	1.11

Source: Hammond, E. C. (*55*).

TABLE 14.—*Percentage of British male cigar smokers who reported inhaling a lot or a fair amount by type of product smoked*

Type of product	1968		1971	
	Number of individuals	Percent	Number of individuals	Percent
Cigars only	706	23.0	111	27.0
Cigars and cigarettes	1,193	42.0	277	44.0
Cigars and pipes	596	35.0	109	32.0
Cigars, cigarettes, and pipes	26	52.0	15	32.0

Source: Todd, G. F. (*93, 94*).

tained somewhat higher levels of cigar smoke inhalation than those cigar smokers who had never smoked cigarettes (30 percent).

Todd (*93*) examined further the relationship between the inhalation of cigarette and cigar smoke. In general, cigarette smokers who switched to cigars were much less likely to report inhaling cigar smoke than cigarette smoke; however, those who in the past reported inhaling cigarette smoke a "lot" or "fair amount" were much more likely to report inhaling cigar smoke to the same degree than those ex-cigarette smokers who in the past did not inhale the smoke of their cigarettes (table 17).

TABLE 15.—*Percentage of individuals reporting inhalation of "almost every puff" of tobacco smoke by current and previous tobacco usage and type of tobacco used*

Type of tobacco smoked		Number of patients	Type inhaled	Percentage inhaled	Confidence limits	
Current usage	Previous usage				Lower	Upper
Cigarettes only	Cigarettes only	2,359	Cigarette	74.8	73.1	76.6
Cigars only	Cigars only	649	Cigars	4.5	3.0	6.0
Cigarettes and cigars.	Cigarettes and cigars.	520	do	20.4	10.5	28.0
Cigars	Cigarettes and cigars.	93	do	18.3	9.0	30.0
None	Cigarettes and cigars.	186	do	21.5	17.8	24.2
Cigars	Cigarettes only	64	do	17.2	16.0	28.0

Source: Bross, I. D. J., Tidings, J. (*14*).

TABLE 16.—*Percentage of British males who reported inhaling a lot or fair amount of cigar smoke by current and previous tobacco usage and type of tobacco previously smoked (1968)*

Type of tobacco smoked		Number of individuals	Type inhaled	Percentage inhaled
Current usage	Previous usage			
Cigarettes only	Cigarettes only	2,586	Cigarette	77.7
Cigars only	Nonsmoker	306	Cigars	18.0
Cigars only	Cigarettes only	321	do	30.0

Source: Todd, G. F. (*94*).

TABLE 17.—*Extent of reported inhalation of cigar smoke by British male cigar smokers who were ex-cigarette smokers in 1968, analyzed by extent of reported inhalation of cigarette smoke when previously smoking cigarettes*

Extent of inhaling cigars	Extent of inhaling cigarettes	
	Inhale a lot or fair amount	Inhale a little or not at all
	Percent	*Percent*
Inhale a lot or fair amount	44. 0	5. 0
Inhale a little or not at all	56. 0	95. 0
Total	100. 0	100. 0
Sample size	244	56

Source: Todd, G. F. (*85*).

Specific Causes of Mortality

Cancer

Several prospective epidemiological studies have shown a significantly higher overall cancer mortality among pipe and cigar smokers compared to the cancer mortality of nonsmokers (table 18).

Pipe and cigar smokers have much higher rates of cancer at certain sites than at others. The upper airway and upper digestive tracts appear to be the most likely target organs. The relationship of pipe and cigar smoking to the development of specific cancers is detailed in the following sections.

TABLE 18.—*Mortality ratios for total cancer deaths in cigar and pipe smokers. A summary of prospective epidemiological studies*

Author, reference	Type of smoking				
	Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only
Hammond and Horn (*40*)	1. 00	1. 34	1. 44	-------	1. 97
Best (*9*)	1. 00	1. 13	1. 38	-------	2. 06
Hammond (*38*)	1. 00	-------	-------	1. 21	1. 76
Kahn (*50*)	1. 00	1. 22	1. 25	1. 25	2. 21

Cancer of the Lip

Approximately 1,500 new cases of cancer of the lip are reported each year. Because of the possibility of early detection and surgical accessibility of cancers in this area, there are less than 200 deaths from cancer of the lip each year in the United States. Some of the earliest scientific investigations exploring the association between tobacco use and disease examined the smoking patterns of individuals with cancer of the lip.

Broders (*13*) in 1920 examined the smoking habits of patients in a retrospective study of 526 cases of epithelioma of the lip and 500 controls. Of the cancer cases, 59 percent smoked pipes, whereas this was true for only 28 percent of the controls. No association was found between cigar or cigarette smoking and cancer of the lip.

In a restrospective study of 439 clinic patients with cancer of the lip and 300 controls conducted in Sweden, Ebenius (*32*) reported a significant association between pipe smoking and cancer of the lip. A total of 61.8 percent of the lip cancer cases smoked pipes, while only 22.9 percent of the controls smoked pipes. No association was found between the use of cigarettes, cigars, or chewing tobacco and cancer of the lip.

In other retrospective studies, Levin, et al. (*60*) reviewed a series of 143 cases of cancer of the lip, and Sadowsky, et al. (*77*) reviewed 571 cases of cancer of the lip. In both studies, a strong association was found between pipe smoking and cancer of the lip. No significant association was found between the use of tobacco in other forms and cancer at this site.

In a study of environmental factors in cancer of the upper alimentary tract, Wynder, et al. (*113*) found an association between pipe smoking, cigarette smoking, and cancer of the lip. There were only 15 cases of cancer of the lip in this study.

Staszewski (*87*) examined the smoking habits of 394 men with carcinoma or precancerous lesions of the lips. An association was found between the smoking of pipes and cigars and cancer of the lip, but this was only of doubtful significance. A significant association was found between the use of cigarettes and cancer of the lip.

Keller (*51*) conducted a study of lip cancers in which he considered a number of factors including histologic types, survival, race, occupations, habits, and associated diseases. A total of 304 patients with primary basal cell or squamous cell carcinoma of the lip and 304 controls from the same hospital matched for age and race were considered in this series. A significant association was found between smoking in all forms and combinations and carcinoma of the lip. It was also found that increasing age and outdoor occupations with exposure to the sun were equally significant factors in the etiology of lip cancer.

In summary, it appears that there are several factors involved in the etiology of cancer of the lip. Among the various forms of tobacco use, pipe smoking either alone or in combination with other forms of smoking seems to be a cause of cancer of the lip. Table 19 summarizes the results of these retrospective studies.

Oral Cancer

The lips, oral cavity, and pharynx are the first tissues exposed to tobacco smoke drawn in through the mouth. Variations in inhalation during the smoking of various tobacco products result in different patterns of distribution of smoke throughout the respiratory tree. However, the oral cavity and adjacent tissues are the sites most consistently exposed to tobacco smoke. For this reason, differences in inhalation should result in less variation in exposure to tobacco smoke for these sites than for the lower trachea and the lung. The inherent carcinogenicity of pipe, cigar, and cigarette smoke is most reliably compared at those tissue sites where dosage and exposure to tobacco smoke are most nearly equal. Data from the epidemiological studies suggest that little difference exists between the smoking of cigarettes, pipes, or cigars and the risk of developing oral cancer.

Hammond and Horn (*40*) examined the association between smoking in various forms and cancer of the combined sites of lip, mouth, pharynx, larynx, and esophagus. The mortality ratios were 5.00 for cigar smokers, 3.50 for pipe smokers, and 5.06 for cigarette smokers compared to nonsmokers. All the deaths from cancer of the lip, oral cavity, and pharynx reported by Doll and Hill (*26*) occurred in smokers. The death rates from cancer at these sites were 0.04 per 1,000 for pipe and cigar smokers, 0.10 per 1,000 for mixed smokers, and 0.05 per 1,000 for cigarette smokers. A fairly detailed analysis of oral cancer was presented by Kahn (*50*) who differentiated between cancer of the oral cavity and cancer of the pharynx. The mortality ratios for oral cancers were 1.00 for those who never smoked, 3.89 for all pipe and cigar smokers, and 4.09 for cigarette smokers. A further breakdown of the pipe and cigar smokers demonstrated a mortality ratio of 4.11 for cigar smokers, 3.12 for pipe smokers, and 4.20 for smokers of pipes and cigars. For cancer of the pharynx, the mortality ratios were 1.00 for those who never smoked, 3.06 for all pipe and cigar smokers, and 12.5 for cigarette smokers. No deaths occurred among those who smoked only cigars. The mortality ratio was 1.98 for pipe smokers and 7.76 for smokers of pipes and cigars. Hammond (*38*) combined cancers of the lip, oral cavity, and pharynx. The pipe and cigar smokers had a mortality ratio of 4.94 and the cigarette smokers a mortality ratio of 9.90 compared to nonsmokers.

TABLE 19.—*Relative risk of lip cancer for men, comparing cigar, pipe, and cigarette smokers with nonsmokers: A summary of retrospective studies*

Author, reference	Number		Relative risk ratio and percentage of cases and controls by type of smoking					
			Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Broders (*13*):		Relative risk	1.0	0.8	4.3	.....	0	.....
Cases	537	Percent cases	7	19	41	.....	1	.....
Controls	500	Percent controls	4	16	6	.....	26	.....
Ebenius (*32*):		Relative risk	1.0	.7	4.1	0.5	.....	.....
Cases	439	Percent cases	49	6	41	4	.....	.....
Controls	300	Percent controls	65	12	13	10	.....	.....
Levin, et al. (*60*):		Relative risk	1.0	1.9	2.9	.....	1.4	.....
Cases	143	Percent cases	15	27	48	.....	45	.....
Controls	554	Percent controls	22	20	24	.....	46	.....
Sadowsky, et al. (*77*):		Relative risk	1.0	1.1	4.3	2.6	1.4	0.4
Cases	571	Percent cases	8	2	18	6	44	22
Controls	615	Percent controls	13	3	7	4	53	19
Wynder,[1] et al. (*118*):		Relative risk	0	.8	1.8	.....	1.0	2.2
Cases	14	Percent cases	0	7	29	.....	36	29
Controls	115	Percent controls	24	9	16	.....	36	13
Staszewski (*87*):		Relative risk	1.0	.....	.....	2.1	2.4	.....
Cases	394	Percent cases	7	.....	.....	12	73	.....
Controls	912	Percent controls	13	.....	.....	11	61	.....
Keller: (*51*):		Relative risk	1.0	1.4	4.0		2.6	
Cases	301	Percent cases	7	2	6	1	60	6
Controls	265	Percent controls	17	4	3	0	53	0

[1] Percentage based on less than 20 patients. Ratios: relative to cigarette smokers.

These studies are summarized in table 20. They demonstrate that smokers experience a large and significant risk of developing cancer of the oral cavity compared to nonsmokers. This risk seems to be about the same for all smokers whether an individual uses a pipe, cigar, or cigarette.

A number of retrospective studies have examined the relationship between smoking in various forms and cancer of the oral cavity. The results of these studies are presented in table 21. Some of the variations in relative risk of developing oral cancer observed in the retrospective studies is probably due to the lack of a uniform definition of oral cancer by anatomical site and the various means used in selecting and defining cases and controls. It appears, however, that a significant risk of developing oral cancer exists for smokers compared to nonsmokers and this risk is similar for smokers of pipes, cigars, and cigarettes.

Several epidemiological investigations have demonstrated an association between the combined use of alcohol and tobacco and the development of oral cancer. A few of these studies (*52*, *62*, *63*, *109*) contain data on pipe and cigar smokers. Heavy smoking and heavy drinking are associated with higher rates of oral cancer than are seen with either habit alone.

TABLE 20.—*Mortality ratios for oral cancer in cigar and pipe smokers. A summary of prospective epidemiological studies*

Author, reference	Smoking type					
	Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Hammond and Horn[1] (*40*)	1.00	5.00	3.50	----	5.06	----
Doll and Hill[2] (*26, 27*)	0.00	----	----	0.80	1.00	2.00
Hammond (*38*)	1.00	----	----	4.94	[3] 9.90	----
Kahn (*60*):						
Oral [4]	1.00	4.11	3.12	3.89	4.09	----
Pharynx	1.00	----	1.98	3.06	12.54	----

[1] Combines data for oral, larynx, and esophagus.
[2] Ratios: relative to cigarette smokers.
[3] Mortality ratios for ages 45 to 64 only are presented.
[4] Excludes pharynx.

Cancer of the Larynx

The larynx is situated at the upper end of the trachea. Because of its proximity to the oral cavity, the larynx probably has a similar exposure to smoke drawn through the mouth as the buccal cavity and pharynx. Tobacco smoke that is not inhaled may still reach as far as the larynx and upper trachea. Pipe and cigar smokers develop cancer of the larynx at rates comparable to those of cigarette smokers. These

TABLE 21.—*Relative risk of oral cancer for men, comparing cigar, pipe, and cigarette smokers with nonsmokers. A summary of retrospective studies*

Author, reference	Number		Relative risk ratio and percentage of cases and controls by type of smoking					
			Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Mills and Porter (*66*):		Relative risk	1.0	----------	----------	7.0	4.1	----------
Cases	124	Percent cases	10	----------	----------	55	36	----------
Controls	185	Percent controls	38	----------	----------	30	32	----------
Sadowsky, et al. (*77*):		Relative risk	1.0	2.0	4.4	----------	1.4	2.1
Cases	1,136	Percent cases	8	4	18	----------	42	28
Controls	615	Percent controls	13	3	7	----------	53	23
Schwartz, et al. (*83*):		Relative risk	1.0	----------	1.6	----------	1.5	----------
Cases	332	Percent cases	16	----------	3	----------	63	----------
Controls	608	Percent controls	23	77	3	----------	58	----------
Wynder, et al. (*109*):		Relative risk	1.0	3.6	6.1	----------	3.0	3.3
Cases	543	Percent cases	3	20	11	----------	57	8
Controls	207	Percent controls	10	13	6	----------	63	8
Wynder, et al. (*113*):		Relative risk	1.0	1.7	.9	----------	1.2	1.4
Cases	115	Percent cases	23	13	12	----------	37	16
Controls	115	Percent controls	26	9	16	----------	36	13

Wynder, et al. (*116*):		Relative risk	1.0	6.0	--------	--------	4.0	---------
Cases	178	Percent cases	4	33	--------	--------	45	---------
Controls	220	Percent controls	16	22	--------	--------	45	---------
Pernu (*73*):		Relative risk	1.0	--------	3.6	--------	2.2	2.9
Cases	1,400	Percent cases	21	--------	10	--------	59	11
Controls	713	Percent controls	39	--------	5	--------	50	7
Staszewski (*87*):		Relative risk	1.0	--------	--------	3.5	3.6	---------
Cases	383	Percent cases	6	--------	--------	13	72	---------
Controls	912	Percent controls	17	--------	--------	11	61	---------
Keller (*52*):		Relative risk	1.0	3.1	3.8	2.2	3.4	---------
Cases	408	Percent cases	5	7	4	10	69	---------
Controls	408	Percent controls	14	6	3	13	56	---------
Martinez (*62*):		Relative risk	1.0	1.7	1.3	--------	1.5	2.3
Cases	170	Percent cases	8	10	1	--------	39	34
Controls	510	Percent controls	14	10	2	--------	44	25
Martinez [1] (*63*):		Relative risk	1.0	2.0	2.8	--------	1.7	2.5
Cases	346	Percent cases	12	10	15	--------	34	34
Controls	346	Percent controls	22	9	1	--------	36	25

[1] This study combines data for oral cancer and cancer of the esophagus.

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rates are several times the rates of nonsmokers. The similarity of the mortality ratios of cancer of the larynx for smoking in various forms suggests that the carcinogenic potentials of the smoke from cigars, pipes, and cigarettes are quite alike at this site.

Several of the prospective epidemiological studies include data on deaths from cancer of the larynx for pipe and cigar smokers as well as for cigarette smokers. Hammond and Horn (*40*) combined data for cancer of the larynx with cancer of the esophagus and oral cavity. The mortality ratios compared to nonsmokers were 5.00 for cigar smokers, 3.50 for pipe smokers, and 5.06 for cigarette smokers. There were no deaths from carcinoma of larynx among nonsmokers in the study of British physicians by Doll and Hill (*26*); however, the death rate for cancer of the larynx among pipe and cigar smokers was 0.10 per 1,000 while the death rate for cigarette smokers was 0.05 per 1,000. Kahn (*50*) reported mortality ratios for cancer of the larynx of 10.33 for cigar smokers, 9.44 for pipe and cigar smokers, 7.28 for all pipe and cigar categories combined, and 9.95 for cigarette smokers. No deaths from cancer of the larynx occurred in pipe smokers. Hammond (*38*) reported a mortality ratio of 3.37 for all pipe and cigar smokers and a mortality ratio of 6.09 for cigarette smokers in the age category 45 to 64. These studies are summarized in table 22.

Several retrospective studies have examined the smoking habits of patients with cancer of the larynx and appropriately matched controls. The small number of pipe and cigar smokers in each study results in relative risk ratios that are quite unstable; however, it appears that pipe and cigar smokers experience a risk of developing cancer of the larynx that is similar to the risk observed among cigarette smokers (table 18).

TABLE 22.—*Mortality ratios for cancer of the larynx in cigar and pipe smokers. A summary of prospective epidemiological studies*

Author, reference	Smoking type					
	Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Hammond and Horn [1] (*40*)	1.00	5.00	3.50	----	5.06	----
Doll and Hill [2] (*26, 27*)	0.00	----	----	2.00	1.00	0.60
Hammond (*38*)	1.00	----	----	3.37	[3] 6.09	----
Kahn (*50*)	1.00	10.33	----	7.28	9.95	----

[1] Combines data for oral, larynx, and esophagus.
[2] Ratios: relative to cigarette smokers.
[3] Only mortality ratios for ages 45 to 64 are presented.

Wynder, et al. (*108*, *113*) distinguished between intrinsic and extrinsic larynx cancers. For smokers the relative risk of developing cancer of the intrinsic larynx was similar to the relative risk of lung cancer whereas the relative risk of developing extrinsic larynx cancer was more like the relative risk of cancer of the upper digestive tract.

Histologic changes of the larynx in relation to smoking in various forms were described by Auerbach, et al. (*5*). Microscopic sections of the larynx from 942 subjects were examined for the presence of atypical nuclei and proliferation of cell rows. Sections were taken from four separate areas of the larynx in each case. Among those who smoked cigars and pipes but not cigarettes, only 1 percent had no atypical cells and more than 75 percent of the subjects had lesions with 50 to 69 percent atypical cells. Four of the cigar and pipe smokers had carcinoma *in situ* and in one of these four cases early invasion was seen in three of the sections. Of those who never smoked regularly, 75 percent had no atypical cells. The cigar and pipe smokers had a similar percentage of cells with atypical nuclei as cigarette smokers who smoked one to two packs per day. With respect to the proliferation of cell rows in the basal layer of the true vocal cord, the least proportion of cases with eight or more cell rows was found in men who never smoked, and the greatest proportion was found in heavy cigarette smokers. Pipe and cigar smokers had a distribution of cell rows that was comparable to that of cigarette smokers who consumed about a pack a day.

Several retrospective studies have reported an association between the combined use of tobacco and alcohol and cancer of the larynx. A study by Wynder, et al. (*108*) included some information on pipe and cigar smoking in relation to drinking habits and the development of cancer of the larynx, but because of the limited number of pipe and cigar smoking subjects this relationship could not be adequately determined.

Cancer of the Esophagus

The esophagus is not directly exposed to tobacco smoke drawn into the mouth; however, the esophagus does have contact with that portion of tobacco smoke that is condensed on the mucous membranes of the mouth and pharynx and then swallowed. The esophagus is also exposed to a portion of tobacco smoke that is deposited in the mucus cleared from the lung by the ciliary mechanism or by coughing. Variations in inhalation of a tobacco product may not appreciably alter the exposure the esophagus receives from smoke dissolved in mucus and saliva. This suggestion receives support from the prospective and retrospective epidemiological studies which demonstrate similar mortality rates for cancer of the esophagus in smokers of cigars, pipes, and cigarettes.

TABLE 23.—*Relative risk of cancer of the larynx for men, comparing cigar, pipe, and cigarette smokers with nonsmokers. A summary of retrospective studies*

Author, reference	Number	Relative risk ratio and percentage of cases and controls by type of smoking						
			Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Schrek, et al. (*81*):		Relative risk	1.0	0	1.1	----------	2.3	----------
Cases	73	Percent cases	14	0	7	----------	80	----------
Controls	522	Percent controls	24	10	11	----------	59	----------
Sadowsky, et al. (*77*):		Relative risk	1.0	2.2	2.3	----------	3.7	4.1
Cases	273	Percent cases	4	2	5	----------	60	29
Controls	615	Percent controls	13	3	7	----------	53	23
Wynder, et al. (*108*):		Relative risk	1.0	15.5	27.7	11.1	24.6	----------
Cases	209	Percent cases	.5	8	5	1	86	----------
Controls	209	Percent controls	11	10	4	2	74	----------
Wynder, et al. (*113*):		Relative risk	1.0	9.7	4.5	----------	6.3	6.3
Cases	60	Percent cases	5	17	15	----------	47	17
Controls	271	Percent controls	24	9	16	----------	36	13
Wynder, et al. (*116*):		Relative risk	1.0	14.5	16.0	----------	22.0	16.0
Cases	142	Percent cases	1	20	1	----------	62	16
Controls	220	Percent controls	16	22	1	----------	45	16

Pernu (*73*):		Relative risk	1.0		4.5		8.7	3.2
Cases	546	Percent cases	7		4		78	4
Controls	713	Percent controls	39		5		50	7
Staszewski (*87*):		Relative risk	1.0			5.9	50.2	
Cases	207	Percent cases	.5			2	88	
Controls	912	Percent controls	17			11	61	
Svoboda (*90*):		Relative risk	1.0		2.6		10.0	
Cases	205	Percent cases	3		3		95	
Controls	320	Percent controls	22		7		71	
Stell (*88*):		Relative risk	1.0			1.3	2.4	
Cases	190	Percent cases	11			8	79	
Controls	190	Percent controls	17			10	50	

In the prospective epidemiological studies, cigar, pipe, and cigarette smokers all had similar mortality ratios from cancer of the esophagus. Hammond and Horn (*40*) combined the categories of carcinoma of the esophagus, larynx, pharynx, oral cavity, and lip and described mortality ratios of 5.00 for cigar smokers, 3.50 for pipe smokers, and 5.06 for cigarette smokers. Doll and Hill (*26*) reported an esophageal cancer mortality ratio of 2.0 for pipe and cigar smokers, 4.8 for mixed smokers, and 1.5 for cigarette smokers. Kahn (*50*) reported the following mortality ratios for smoking in various forms compared to nonsmokers: cigar only, 5.33; pipe only, 1.99; pipe and cigar, 4.17; all pipes and cigars combined, 4.05; and cigarettes only, 6.17. The results of these prospective studies are summarized in table 24.

Several retrospective investigations have also examined the association between smoking in various forms and cancer of the esophagus. These studies have been summarized in table 25. The evidence suggests that cigar, pipe, and cigarette smokers develop cancer of the esophagus at rates substantially higher than those seen in nonsmokers, and that little difference exists between these rates observed in smokers of pipes and cigars and cigarettes.

Histologic changes in the esophagus in relation to smoking in various forms were investigated by Auerbach, et al. (*7*), who looked for atypical nuclei, disintegrating nuclei, hyperplasia, and hyperactive esophageal glands. A total of 12,598 sections were made from tissues obtained from 1,268 subjects. For each of the parameters investigated, pipe and cigar smokers demonstrated significantly more abnormal histologic changes than nonsmokers; however, these changes were not as severe or as frequent as those seen in cigarette smokers.

Several retrospective studies conducted in the United States and other countries have examined the synergistic roles of tobacco use and heavy alcohol intake on the development of cancer of the esophagus. Four of these investigations contain data on pipe and cigar smoking (*12, 62, 63, 107*). It appears that smoking in any form in combination with heavy drinking results in especially high rates of cancer of the esophagus.

TABLE 24.—*Mortality ratios for cancer of the esophagus in cigar and pipe smokers. A summary of prospective epidemiological studies*

Author, reference	Smoking type					
	Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Hammond and Horn [1] (*40*)	1.00	5.00	3.50	.....	5.06	.....
Doll and Hill (*26, 27*)	1.00	.....	.....	2.00	1.50	4.80
Hammond (*38*)	1.00	.....	.....	3.97	[2] 4.17	.....
Kahn (*50*)	1.00	5.33	1.99	4.05	6.17	.....

[1] Combines data for oral, larynx, and esophagus.
[2] Mortality ratio for ages 45 to 64.

TABLE 25.—*Relative risk of cancer of the esophagus for men, comparing cigar, pipe, and cigarette smokers with nonsmokers. A summary of retrospective studies*

Author, reference	Number	Relative risk ratio and percentage of cases and controls by type of smoking					
			Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Sadowsky, et al. (*77*):		Relative risk	1.0	4.8	3.8	5.1	3.8	3.3
Cases	104	Percent cases	4	5	8	6	60	18
Controls	615	Percent controls	13	3	7	4	53	19
Wynder, et al. (*113*):		Relative risk	1.0	3.1	2.1	----	2.6	.4
Cases	39	Percent cases	13	15	18	----	51	3
Controls	115	Percent controls	24	9	16	----	36	13
Pernu (*73*):		Relative risk	1.0	----	3.0	----	2.7	5.9
Cases	202	Percent cases	17	----	7	----	59	18
Controls	713	Percent controls	39	----	5	----	50	7
Schwartz, et al. (*84*):		Relative risk	1.0	----	2.6	----	11.7	8.6
Cases	249	Percent cases	2	----	2	----	88	7
Controls	249	Percent controls	18	----	7	----	67	7
Wynder and Bross (*107*):		Relative risk	1.0	3.6	9.0	6.0	2.8	3.7
Cases	150	Percent cases	5	19	9	4	51	11
Controls	150	Percent controls	15	16	3	2	55	9

TABLE 25—*Relative risk of cancer of the esophagus for men, comparing cigar, pipe, and cigarette smokers with nonsmokers. A summary of retrospective studies.*—Continued

Author reference	Number	Relative risk ratio and percentage of cases and controls by type of smoking					
			Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Bradshaw and Schonland (*12*):		Relative risk	1.0	----------	4.8	--------	2.3	----------
Cases	117	Percent cases	15	----------	41	--------	63	----------
Controls	366	Percent controls	32	----------	18	--------	58	----------
Martinez (*62*):		Relative risk	1.0	2.0	--------	--------	1.5	2.2
Cases	120	Percent cases	8	9	--------	--------	31	43
Controls	360	Percent controls	14	8	--------	--------	34	34
Martinez [1] (*63*):		Relative risk	1.0	2.0	2.8	--------	1.7	2.5
Cases	346	Percent cases	21	10	15	--------	34	34
Controls	346	Percent controls	22	9	1	--------	36	25

[1] This study combines data for oral cancer and cancer of the esophagus.

Abundant evidence has accumulated from epidemiological, experimental, and autopsy studies establishing that cigarette smoking is the major cause of lung cancer. Several prospective epidemiological studies have demonstrated higher lung cancer mortality ratios for pipe and cigar smokers than for nonsmokers, but the risk of developing lung cancer for pipe and cigar smokers is less than for cigarette smokers. Table 26 presents a summary of these prospective studies. Dose-response relationships such as those that helped demonstrate the nature of the association between cigarette use and lung cancer could not be as thoroughly studied for pipe and cigar smokers because of the relatively few smokers in these categories. Although the number of deaths were few, Doll and Hill (*26*) reported increased death rates from lung cancer for pipe and cigar smokers with increasing tobacco consumption (table 27). Kahn (*50*) also demonstrated a dose-response relationship for lung cancer by the amount smoked (table 28).

A few of the retrospective studies contained enough smokers to allow an examination of dose-response relationships for pipe and cigar smoking and lung cancer (*1*, *61*, *74*, *77*). An increased risk of developing lung cancer was demonstrated with the increased use of pipes and cigars as measured by amount smoked and inhalation. The retrospective investigation of Abelin and Gsell (*1*) is of particular interest. The smoking habits of 118 male patients with cancer of the lung from a rural area of Switzerland were compared with those reported in a survey of all male inhabitants of a town in the same region. About 20 percent of the population of this area were regular cigar smokers, the most popular cigar being the Stümpen, a small Swiss-made machine-manufactured cigar cut at both ends with an average weight of 4.5 g. In this investigation, cigar smokers experienced a risk of developing lung cancer that was similar to the risk of cigarette smokers. A dose-response relationship was demonstrated for inhalation and amount smoked. These data suggest that the heavy smoking of certain cigars may result in a risk of lung cancer that is similar to that experienced by cigarette smokers.

Several pathologists have reported histologic changes in the bronchial epithelium in relation to smoking in various forms. Knudtson (*57*) examined the bronchial mucosa of 150 lungs removed at autopsy and correlated the histologic changes noted with the history of smoking, age, occupation, and residence. Specimens obtained from the six cigar and pipe smokers demonstrated basal cell hyperplasia; however, there was no squamous or atypical proliferative metaplasia as is frequently seen in the heavy cigarette smokers.

Sanderud (*78*) examined histologic sections from the bronchial tree of 100 male autopsy cases for the presence of squamous epithelial

metaplasia. In this study, 39 percent of the population were nonsmokers, 20 percent were pipe smokers, and 38 percent smoked cigarettes. A total of 80 percent of the pipe smokers and cigarette smokers demonstrated squamous metaplasia of the bronchial tree, whereas only 5½ percent of the nonsmokers had this abnormality.

Auerbach, et al. (*6*) examined 36,340 histologic sections obtained from 1,522 white adults for various epithelial lesions including: presence or absence of ciliated cells, thickness or number of cell rows, atypical nuclei, and the proportion of cells of various types. The pathologic findings in the bronchial epithelium of pipe and cigar smokers are compared to those found in nonsmokers and cigarette smokers (table 25). Pipe and cigar smokers had abnormalities that were intermediate between those of nonsmokers and cigarette smokers, although cigar smokers had pathologic changes that in some categories approached the changes seen in cigarette smokers.

TABLE 26.—*Mortality ratios for lung cancer deaths in male cigar and pipe smokers. A summary of prospective studies*

Author, reference	Type of smoking					
	Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Hammond and Horn (*40*)	1.00	3.35	8.50	----	23.12	19.71
Doll and Hill (*26, 27*)	1.00	----	----	6.14	13.29	7.43
Best (*9*)	1.00	2.94	4.35	----	14.91	----
Hammond (*38*)	1.00	1.85	2.24	1.97	9.20	7.39
Kahn (*50*)	1.00	1.59	1.84	1.67	12.14	----

TABLE 27.—*Lung cancer death rates for cigar and pipe smokers by amount smoked—Doll and Hill*

Smoking type	Death rate per 100	Number of deaths
Nonsmoker	0.07	3
Cigar and pipe:		
1 to 14 g. per day	.42	12
15 to 24 g. per day	.45	6
>24 g. per day	.96	3
Cigarette only	.96	143

Source: Doll, R., Hill, A. B. (*26*).

TABLE 28.—*Lung cancer mortality ratios for cigar and pipe smokers by amount smoked—Kahn*

Smoking type	Mortality ratio	Number of deaths
Nonsmoker	1.00	78
Cigar smokers:		
<5 cigars per day	1.14	12
5 to 8 cigars per day	2.64	11
>8 cigars per day	2.07	2
Pipe smokers:		
<5 pipefuls per day	.77	2
5 to 19 pipefuls per day	2.20	12
>19 pipefuls per day	2.47	3
Cigar and pipe:		
8 or less cigars, 19 or less pipefuls	1.62	18
>8 cigars, >19 pipefuls	2.19	2

Source: Kahn, H. A. (*50*).

TABLE 29.—*Relative risk of lung cancer for men, comparing cigar, pipe, and cigarette smokers with nonsmokers. A summary of retrospective studies*

Author, reference	Number	Relative risk ratio and percentage of cases and controls by type of smoking						
			Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Levin, et al. (*60*):		Relative risk	1.0	0.7	0.8	.....	2.1	.....
Cases	236	Percent cases	15	11	14	.....	66	.....
Controls	481	Percent controls	22	23	25	.....	44	.....
Schrek, et al. (*81*):		Relative risk	1.0	.6	.7	.....	1.7	.....
Cases	82	Percent cases	15	4	5	.....	61	.....
Controls	522	Percent controls	22	23	11	.....	59	.....
Wynder and Graham (*111*):		Relative risk	1.0	5.1	3.6	.....	15.7	.....
Cases	605	Percent cases	1	4	4	.....	91	.....
Controls	780	Percent controls	15	8	12	.....	65	.....
Doll and Hill (*25*):		Relative risk	1.0	.....	5.1	.....	9.6	.....
Cases	1,357	Percent cases	.5	.....	4	.....	74	.....
Controls	1,357	Percent controls	5	.....	7	.....	69	.....
Koulumies (*56*):		Relative risk	1.0	.....	9.6	.....	29.3	.....
Cases	812	Percent cases	.6	.....	2	.....	77	.....
Controls	300	Percent controls	18	.....	6	.....	76	.....
Sadowsky, et al. (*77*):		Relative risk	1.0	2.4	1.4	.....	3.7	5.6
Cases	477	Percent cases	4	2	3	.....	57	31
Controls	615	Percent controls	13	3	7	.....	53	19

Wynder and Cornfield (*110*):		Relative risk	1.0	2.5	4.0		8.5		
Cases	63	Percent cases	4	13	6		77		
Controls	133	Percent controls	21	27	8		45		
Randig (*74*):		Relative risk	1.0	5.3	5.0		5.0		
Cases	415	Percent cases	1	21	11		67		
Controls	381	Percent controls	6	19	11		64		
Mills and Porter (*66*):		Relative risk	1.0			6.0	5.4		
Cases	444	Percent cases	7			37	55		
Controls	430	Percent controls	31			26	43		
Mills and Porter (*66*):		Relative risk	1.0			2.8	4.5		
Cases	484	Percent cases	8			13	78		
Controls	1,588	Percent controls	28			16	57		
Schwartz and Denoix (*82*):		Relative risk	1.0		4.7		13.5		
Cases	430	Percent cases	1		6		96		
Controls	430	Percent controls	11		14		78		
Stocks (*89*):		Relative risk	1.0		3.1		5.0		
Cases	2,101	Percent cases	2		9		89		
Controls	5,960	Percent controls	9		13		78		
Lombard and Snegireff (*61*):		Relative risk	1.0			1.7	8.1		
Cases	500	Percent cases	2			4	95		
Controls	1,839	Percent controls	10			15	75		
Pernu (*73*):		Relative risk	1.0		4.2		9.2	11.1	
Cases	1,477	Percent cases	7		4		77	13	
Controls	713	Percent controls	39		5		50	7	

TABLE 29.—*Relative risk of lung cancer for men, comparing cigar, pipe, and cigarette smokers with nonsmokers. A summary of retrospective studies*—Continued

Author, reference	Number		Relative risk ratio and percentage of cases and controls by type of smoking					
			Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Wicken (*106*):		Relative risk	1.0	----------	--------	2.2	4.3	4.2
Cases	803	Percent cases	4	----------	--------	10	78	7
Controls	803	Percent controls	14	----------	--------	16	64	6
Abelin and Gsell (*1*):		Relative risk	1.0	30.7	21.8	39.9	31.0	24.7
Cases	118	Percent cases	2	28	7	58	25	24
Controls	524	Percent controls	35	19	6	31	17	10
Wynder, et al. (*115*):		Relative risk	1.0	----------	--------	2.0	12.4	----------
Cases	210	Percent cases	3	----------	--------	5	92	----------
Controls	420	Percent controls	21	----------	--------	15	47	----------

TABLE 30.—*Changes in bronchial epithelium of male cigar, pipe, and cigarette smokers as compared to nonsmokers*

Group	Number of subjects	Sections with epithelium	Percent sections with epithelial lesions	Percent 3 plus cell rows with cilia	Percent atypical cells present	Total sections	Percent hyperplasia and goblet cells in glands
1st set (none vs. pipe vs. cigarette—matched on 1:1 basis):							
Nonsmoker	20	985	21.7	11.2	2.6	1,031	10.3
Pipe only	20	924	65.5	38.1	37.0	979	35.9
Cigarette only	20	914	96.8	88.6	95.2	982	72.1
2d set (none vs. pipe vs. cigarette—matched on frequency basis):							
Nonsmoker	25	1,246	22.9	13.4	.7	1,277	11.5
Pipe only	25	1,164	68.7	38.7	38.2	1,247	37.9
Cigarette only	25	1,126	96.3	88.7	89.5	1,237	75.5
3d set (none vs. cigar vs. cigarette):							
Nonsmoker	35	1,706	27.4	12.7	.8	1,748	15.3
Cigar only	35	1,733	90.8	40.0	73.6	1,828	52.5
Cigarette only	35	1,526	99.0	92.7	97.8	1,693	80.2

Source: Auerbach et al. (6).

Tumorigenic Activity

The tumorigenic activity of tobacco smoke can be modified in both a quantitative and qualitative sense. Physical or chemical changes in tobacco that result in a reduction of total particulate matter upon combusion of a given quantity of tobacco may result in a reduction of carcinogenic potential. Such factors as tobacco selection, treatment, blending, cut, and additives may quantitatively alter tar production. Wrapper porosity and filtration may also affect tar production.

Quantitative changes in the tumorigenic activity of tobacco tar on a gram-for-gram basis can be produced by the selection and treatment of tobacco, the use of additives or tobacco sheets, or adjustments in the cut and packing density.

Combustion temperature can also produce quantitative changes in the particulate matter of tobacco smoke. Although high-temperature burning produces less particulate matter in the smoke, it appears that tumorigenic components occur in higher concentration when tobacco is pyrolized at temperatures higher than 700° centigrade (*34*).

Cigars, pipes, and cigarettes are similar in that they are smoked orally and have a common site of introduction to the body. The tissues of the mouth, larynx, pharynx, and esophagus appear to receive approximately equal exposure to the smoke of these products. Inhalation causes smoke to be drawn deeply into the lungs and also allows for systemic absorption of certain constituents of tobacco smoke which then can be carried further to other organs.

Pipe tobacco and cigars vary from cigarettes in a number of characteristics that can produce both quantitative and qualitative changes in the total particulate matter produced by their combustion. Experimental evidence suggests that although there is some difference in the amount and quality of tar produced by cigars, this cannot account for the reduced mortality observed in cigar smokers compared to cigarette smokers.

Experimental Studies

Several experimental investigations have been conducted to examine the relative tumorigenic activity of tobacco smoke condensates obtained from cigarettes, cigars, and pipes. Most of these studies were standardized in an attempt to make the results of the cigar and pipe experiments more directly comparable with the cigarette data and most used the shaved skin of mice for the application of tar. Tars from cigars, pipes, and cigarettes were usually applied on an equal weight basis so that qualitative differences in the tars could be determined. In several experiments, the nicotine was extracted from the pipe and cigar condensates in an attempt to reduce the acute toxic effects that resulted in animals from the high concentrations of nicotine frequently found in these products.

Wynder and Wright (*117*) examined the differences in tumorigenic activity of pipe and cigarette condensates. Tars were obtained by the smoking of a popular brand of king-size cigarettes and the same cigarette tobacco smoked in 12 standard-grade briar bowl pipes. Both the cigarettes and pipes were puffed three times a minute with a 2-second puff and a 35-ml. volume. Both the cigarettes and pipes attained similar maximum combustion zone temperatures; however, the use of cigarette tobacco in the pipe resulted in a combustion chamber temperature that averaged about 150° centigrade higher than temperatures achieved when pipe tobacco was used. Chemical fractionation was accomplished and equal concentrations of the neutral fraction were applied in three weekly applications to the shaved skin of CAF_1 and Swiss mice. The results indicate that neutral tar obtained from cigarette tobacco smoked in pipes is more active than that obtained in the usual manner from cigarettes. About twice as many cancers were obtained in both the CAF_1 and the Swiss mice, and the latent period was about 2 months shorter.

Extending these data, Croninger, et al. (*20*) examined the biologic activity of tars obtained from cigars, pipes, and cigarettes. Each form of tobacco was smoked as it was manufactured in a manner to simulate human smoking or to maintain tobacco combustion. The whole tar was applied in dilutions of one-to-one and one-to-two with acetone to the shaved backs of female CAF_1 and female Swiss mice using three applications each week for the life-span of the animal. The nicotine was extracted from the pipe and cigar condensates to reduce the acute toxicity of the solutions. The Swiss mice, pipe, cigar, and cigarette tars produced both benign and malignant tumors. The incidence rates of malignant tumors given as percents were: 44, 41, and 37, respectively. These results suggested a somewhat higher degree of carcinogenic activity for cigar and pipe tars than for cigarette tar.

Similar results were reported by Kensler (*53*) who applied condensates obtained from cigars and cigarettes to the shaved skin of mice. The incidence of papillomas produced by cigar smoke concentrate was no different from that of the cigarette smoke condensate. Similarly, there was no difference between cigar and cigarette smoke condensates when carcinoma incidences were compared.

Homburger, et al. (*45*) prepared tars from cigar, pipe, and cigarette tobaccos that were smoked in the form of cigarettes. In this way, all tobaccos were smoked in an identical manner and uniform combustion temperatures were achieved. Because of this standardization, differences in tumor yield could be attributed to tobacco blend and not the manner in which the tars were prepared. The whole tars were diluted one-to-one with acetone and applied to the shaved skin of CAF_1 mice three times a week for the lifespan of the test animal. Skin cancers were produced more quickly with pipe and cigar smoke condensates than with cigarette smoke condensates. This suggests that the smoking

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of pipe and cigar tobaccos in the form of cigarettes does not alter the condensates to any significant degree.

Davies and Day (*22*) prepared tars from small cigars especially manufactured from a composite blend of cigar tobacco representing small cigar brands smoked in the United Kingdom, cigarettes especially manufactured from the same tobacco used for the cigars described above, and plain cigarettes especially manufactured from a composite blend of flue-cured tobacco representing the major plain cigarette brands smoked in the United Kingdom. The whole tar was diluted to four concentration levels and applied to the shaved backs of female albino mice for their lifespan using four dosing regimens. A statistically significant increase in mouse skin carcinogenicity was shown with the cigar smoke condensate compared with the tars obtained from either flue-cured or cigar tobacco cigarettes. These results are consistent with those of the previously reported investigations.

The effect of curing on carcinogenicity was examined by Roe, et al. (*76*). Bright tobacco grown in Mexico was either flue-cured or air-cured and bulk fermented. Both flue-cured and air-cured tobaccos were made into cigarettes standardized for draw resistance and were smoked under similar conditions. Condensates from these cigarettes were applied to mouse skin three times each week in an acetone solution. The development of skin tumors was higher in mice treated with the flue-cured condensate than in mice treated with the air-cured condensate ($P<0.01$). The difference may have been due to the use of equal weights of condensate rather than the use of extracts from an equal number of cigarettes. The air-cured cigarettes produced a greater weight of condensate than did the flue-cured cigarettes. A chemical analysis of the two tobaccos and two condensates revealed only small differences in composition. Evidently air curing of Bright tobacco in the method used is not associated with a loss of reducing sugars.

A more detailed analysis of these experimental studies is presented in table 31.

These experimental data suggest that cigar and pipe tobacco condensates have a carcinogenic potential that is comparable to cigarette condensates. This is supported by human epidemiological data for those sites exposed equally to the smoke of cigars, pipes, and cigarettes. The partially alkaline smoke derived from pipes and cigars is generally not inhaled, and as a result there appears to be a lower level of exposure of the lungs and other systems to the harmful properties of pipe and cigar smoke than occurs with cigarette smoking. It is anticipated that modifications in pipe tobacco or cigars which would result in a product that was more readily inhalable would eventually result in elevated mortality from cancer of the lung, bronchitis and emphysema, arteriosclerotic cardiovascular diseases, and the other conditions which have been clearly associated with cigarette smoking.

TABLE 31.—*Tumorigenic activity of cigar, pipe, and cigarette smoke condensates in skin painting experiments on animals*

[Key: A = Method. B = Frequency. C = Duration. D = Material.]

Author, reference	Animal	Activity	Treatment	Number	Percent	
					Papillomas	Carcinomas
Wynder and Wright (*117*).	CAF_1 and Swiss mice.	A. Painting shaved skin. B. 3 times a week. C. Lifespan (24 months). D. Neutral fraction tar from cigarettes and cigarette tobacco smoked in pipes.	CAF_1: Pipe (cigarette tobacco) Cigarette Swiss: Pipe (cigarette tobacco) Cigarette	30 30 30 30	60 30 63 63	20 3 50 33
Croninger, et al. (*20*).	Female Swiss mice.	A. Painting shaved skin. B. 3 times a week. C. Lifespan. D. Whole tar diluted in acetone.	Cigar, nicotine free (1:1) Pipe, nicotine free (1:1) Cigar (1:2) Pipe, nicotine free (1:2) Cigarette (1:1) Acetone controls	46 45 78 89 86 23	65 71 33 30 47 0	41 44 18 16 37 0
Kensler (*53*)	Swiss mice	A. Painting shaved skin. B. 3 times a week. C. Lifespan. D. Whole tar diluted in acetone.	Cigar tar (J) 100 mg. per week Cigarette tar (G) 100 mg. per week. Cigarette tar (E) 100 mg. per week.	100 100 100	42 40 34	41 28 34

TABLE 31.—*Tumorigenic activity of cigar, pipe, and cigarette smoke condensates in skin painting experiments on animals*—Continued

[Key: A = Method. B = Frequency. C = Duration. D = Material.]

Author, reference	Animal	Activity	Treatment	Number	Percent	
					Papillomas	Carcinomas
Homburger, et al. (*46*).	CAF_1 mice	A. Painting shaved skin. B. 2 to 3 times a week. C. Lifespan (2 years). D. Whole tar diluted 50 percent in acetone.	Cigar tobacco cigarettes [1] 65 mg. per week.	100	37. 5	19
			Pipe tobacco cigarettes [1] 64 mg. per week.	100	23	20
			Cigarettes [1] 62 mg. per week	100	15	23
			Acetone controls	100	0	0
Davies and Day (*22*).	Female albino mice.	A. Painting shaved skin. B. Varied. C. 116 weeks. D. Whole tar in 150 mg. acetone.	Cigars, small 83 mm. long 150 per week.	144	44	27
			Cigar tobacco cigarettes 150 per week.	72	32	14
			Cigarettes 150 per week	144	28	13
Roe, et al. (*76*).	Female Swiss mice.	A. Painting shaved skin. B. 3 times a week. C. Lifespan. D. Whole tar diluted in acetone.	Flue-cured Bright tobacco 180 mg. per week.	400	52	30
			Air-cured Bright tobacco 180 mg. per week.	400	68	23
			Acetone controls 0.75 cc. per week.	400	1. 3	0. 5

[1] Cigar, pipe, and cigarette tobacco smoked as cigarettes at similar combustion temperatures.

Cardiovascular Diseases

The majority of deaths in the United States each year are due to cardiovascular diseases. Cigarette smoking has been identified as a major risk factor for the development of coronary heart disease (CHD). However, pipe and cigar smokers experience only a small increase in mortality from coronary heart disease above the rates of nonsmokers. Cigarette smokers have higher death rates from cerebrovascular disease than nonsmokers, whereas pipe and cigar smokers have cerebrovascular death rates that are only slightly above the rates of nonsmokers. Table 32 summarizes the major prospective epidemiological investigations that examined the association of smoking in various forms and total cardiovascular diseases, coronary heart disease, and cerebrovascular disease. Doll and Hill. (*28*), Best (*9*), and Kahn (*50*) examined dose-response relationships for pipe and cigar smokers and reported a slight increase in mortality from coronary heart disease with an increase in the number of cigars or pipefuls smoked.

Other prospective epidemiological studies have also examined the relationship of smoking in various forms to coronary heart disease and related risk factors. Jenkins, et al. (*49*) in the Western Collaborative Group Study of coronary heart disease, reported an incidence of coronary heart disease in men aged 50 to 59 who were pipe and cigar smokers that was intermediate between the rates seen in cigarette smokers and nonsmokers. No increase in incidence of coronary heart disease was seen among the pipe and cigar smokers in the younger age groups. Shapiro, et al. (*85*), in a study of the health insurance plan (HIP) population, reported incidence rates for myocardial infarction, angina pectoris, and possible MI, in pipe and cigar smokers that were similar to the incidence rates seen in cigarette smokers. These rates were considerably higher than those of nonsmokers. Data from the pooling project (*47*) suggested that the incidence of CHD deaths, sudden death, and the first major coronary event in pipe and cigar smokers was intermediate between the incidence experienced by cigarette smokers and nonsmokers. In contrast to these studies, Doyle, et al. (*30*) reported no increase in CHD deaths, myocardial infarction, or angina pectoris in pipe and cigar smokers over the rates of nonsmokers in the Framingham study.

The retrospective studies of Mills and Porter (*64*), Villiger and Heyden-Stucky (*104*), Schimmler, et al. (*80*), and Hood, et al. (*46*) contained data suggesting that pipe and cigar smokers experience mortality rates from coronary heart disease that are essentially similar to those experienced by cigarette smokers. The retrospective study of Spain and Nathan (*86*) reported lower rates of coronary heart disease in all smoking categories than were found in nonsmokers.

Van Buchem (*103*) and Dawber, et al. (*23*) examined serum cholesterol levels in groups of individuals classified according to smoking

habits. In these two studies, pipe and cigar smokers had serum cholesterol levels that were nearly identical with the levels found in nonsmokers.

Tibblin (*91*) and Dawber, et al. (*23*) investigated the effect of smoking on blood pressure. The proportion of smokers decreased in groups with higher blood pressures, although this was not as dramatic for pipe and cigar smokers as it was for cigarette smokers.

In an experimental study using anesthetized dogs, Kershbaum and Bellet (*54, 55*) examined the effects of inhaled and noninhaled cigarette, cigar, and pipe smoke on serum free fatty acid levels and urinary catecholamine and nicotine excretion. In this study, inhalation of tobacco smoke from all these sources resulted in similar increases in serum free fatty acids and in catecholamine and nicotine excretion.

TABLE 32.—*Mortality ratios for cardiovascular deaths in male cigar and pipe smokers. A summary of prospective epidemiological studies*

Author, reference	Category	Type of smoking					
		Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Hammond and Horn (*40*).	Cardiovascular total.	1.00	1.26	1.07	------	1.57	------
	Coronary	1.00	1.28	1.03	------	1.70	------
	Cerebrovascular	1.00	1.31	1.23	------	1.30	------
Doll and Hill (*26, 27*).	Cardiovascular total.	1.00	-----	------	0.99	1.26	1.13
	Coronary	1.00	-----	------	.94	1.23	1.18
	Cerebrovascular	1.00	-----	------	.95	1.13	.97
Best (*9*)	Cardiovascular total.	1.00	1.14	.95	------	1.52	------
	Coronary	1.00	.99	1.00	------	1.60	------
	Cerebrovascular	1.00	1.28	.85	------	.88	------
Hammond [1] (*38*).	Cardiovascular total.	1.00	-----	------	1.06	1.90	------
	Coronary	1.00	1.35	1.19	------	1.84	1.58
	Cerebrovascular	1.00	-----	------	1.09	1.41	1.40
Kahn (*50*)	Cardiovascular total.	1.00	1.05	1.06	1.05	1.75	------
	Coronary	1.00	1.04	1.08	1.05	1.74	------
	Cerebrovascular	1.00	1.08	1.09	1.06	1.52	------

[1] Mortality ratios for ages 55 to 64 only are presented.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Chronic bronchitis and pulmonary emphysema account for most of the morbidity and mortality from chronic respiratory disease in the United States. Cigarette smokers have higher death rates from these

diseases and have more pulmonary symptoms and impaired pulmonary function than nonsmokers. Cigarette smokers also have more frequent and more severe respiratory infections than nonsmokers. The relationship between smoking pipes and cigars and these diseases is summarized in this chapter. The major prospective epidemiological studies are summarized in table 33.

In a retrospective study of 1,189 males and matched controls in Northern Ireland, Wicken (*106*) investigated smoking in various forms and mortality from bronchitis. The relative risk ratios compared to nonsmokers for mortality from chronic bronchitis were 1.98 for all smokers, 1.55 for pipe and cigar smokers, 2.25 for cigarette smokers, and 1.49 for mixed smokers.

From a review of these prospective and retrospective studies, it appears that pipe and cigar smokers experience mortality rates from bronchitis and emphysema that are higher than the rates of nonsmokers. Although these morality rates approach those of cigarette smokers, in most instances they are intermediate between the rates of cigarette smokers and nonsmokers.

Pipe and cigar smokers have significantly more respiratory symptoms and illnesses than nonsmokers. Those studies which contain data on pipe and cigar smoking as related to respiratory symptoms are summarized in table 34.

Only a few studies have examined pulmonary function in pipe and cigar smokers. There appears to be little difference in pulmonary function values for pipe and cigar smokers as compared to nonsmokers (table *35*).

Naeye (*67*) conducted an autopsy study on 322 Appalachian coal workers who were classified according to the type of coal mined and tobacco usage. Emphysema was slightly greater in cigarette smokers, as were anatomic evidences of chronic bronchitis and bronchiolitis. Those changes found in pipe and cigar smokers were intermediate between those of cigarette smoking miners and nonsmoking miners.

Changes in pulmonary histology in relation to smoking habits and age were examined by Auerbach, et al. (*8*). Fibrosis, alveolar rupture, thickening of the walls of small arteries, and thickening of the walls of the pulmonary arterioles were found to be highly related to the smoking habits of the 1,340 male subjects examined. The 91 pipe and cigar smokers over the age of 60 were found to have somewhat more alveolar rupture than the men of the same age distribution who never smoked regularly. However, pipe and cigar smokers as a group had far less rupture than cigarette smokers. The same relations as described above were found for fibrosis, thickening of the walls of the arterioles and small arteries, and padlike attachments to the alveolar septums.

Tobacco smoke has been shown experimentally to have a ciliostatic effect on the respiratory epithelium. The interval between puffs, the

amount of volatile and particulate compounds in the smoke, and the exposure volume have been shown to influence the toxic effect of tobacco smoke. Dalhamn and Rylander (*21*) exposed the upper trachea of anesthetized cats to the smoke of cigarettes and cigars, observing the effect on ciliary activity through an incident-light microscope. A chemical analysis of the gas and particulate phases revealed that the cigar smoke was more alkaline and, in general, contained higher concentrations of isoprene, acetone, acetonitrile, toluene, and total particulate matter compared to cigarette smoke. The average number of puffs required to arrest ciliary activity was found to be 73 for the cigarette smoke and 114 for the cigar smoke. The difference is statistically significant ($P < 0.01$). Of the two smokes, the smoke with the highest concentration of volatile compounds was found to be the least ciliostatic. This suggests that the degree of ciliotoxicity of a smoke is not necessarily correlated to the level of one or several of the substances found in the smoke.

Passey, et al. (*70, 71, 72*) studied the effect of smoke from flue-cured cigarette tobacco cigarettes and air-cured cigar tobacco cigarettes on the respiratory system of rats. In two separate but similar experiments, a total of 48 animals were exposed to English cigarette tobacco smoke, 48 were exposed to air-cured cigar tobacco smoke, and 12 were exposed to an air-cured Burley tobacco smoke. The rats in groups were exposed to the specific smoke in a smoke-filled cabinet. Animals exposed to the smoke from air-cured tobaccos remained healthy throughout the experiments, even at high levels of smoke exposure. The three deaths that occurred within this group were from nonrespiratory causes. In both experiments, the rats exposed to cigarette tobacco smoke began to die within 1 or 2 months, and in each experiment most of the animals died within a week or two of the first deaths. At autopsy the rats exposed to flue-cured tobacco smoke on gross examination were found to have greatly enlarged lungs, the trachea was often full of mucus, and there was evidence of pneumonia. On microscopic examination it was found that the trachea and bronchi contained purulent cellular exudates, evidence of metaplastic changes, an absence of cilia, and goblet cell hpyerplasia. Typically, the cause of death was a lobar or bronchopneumonia. The author concluded that, "the smokes of flue-cured tobaccos are more dangerous to man and to animals than those of air-cured tobaccos."

Unfortunately, few details were published concerning the method used to expose the animals to the different types of smoke. The frequency and duration of exposure were not specified, and the extent of actual inhalation of smoke by the different groups of rats was either not determined or not reported. It is also difficult to determine the effect of smoke exposure on the frequency and severity of respiratory infections when animals are exposed to smoke in groups where common exposure occurs. The rat strain used was not identified, but it was noted that animals appeared to suffer from an endemic rat bronchiectasis. It is not known to what extent epidemics of respiratory infections occurred among these animals. Because of these difficulties, no firm conclusion can be drawn concerning the effect of smoking flue-cured or air-cured tobaccos on the incidence of respiratory infections in rats.

TABLE 33.—*Mortality ratios for chronic obstructive pulmonary deaths in male cigar and pipe smokers. A summary of prospective epidemiological studies*

Author, reference	Category	Type of smoking					
		Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Hammond and Horn (*40*).	COPD total	1.00	1.29	1.77	-----	2.85	------
	Emphysema	----	-----	-----	-----	----------	
	Bronchitis	----	-----	-----	-----	----------	
Doll and Hill (*26, 27*).	COPD total	----	-----	-----	-----	----------	
	Emphysema	----	-----	-----	-----	----------	
	Bronchitis	1.00	-----	-----	4.00	7.00	6.67
Best (*9*)	COPD total	----	-----	-----	-----	----------	
	Emphysema	1.00	3.33	.75	-----	5.85	------
	Bronchitis	1.00	3.57	2.11	-----	11.42	------
Hammond (*38*)	COPD total	----	-----	-----	-----	----------	
	Emphysema	1.00	-----	-----	1.37	[1] 6.55	------
	Bronchitis	----	-----	-----	-----	----------	
Kahn (*60*)	COPD total	1.00	.79	2.36	.99	10.08	------
	Emphysema	1.00	1.24	2.13	1.31	14.17	------
	Bronchitis	1.00	1.17	1.28	1.17	4.49	------

[1] Only mortality ratios for ages 55 to 64 are presented.

TABLE 34.—*Prevalence of respiratory symptoms and illness by type of smoking*

Author, reference	Number and type of population	Illness	Percent prevalence			
			Non-smoker	Total pipe and cigar	Cigarette only	Mixed
Boake (*10*)	Parents of 59 families.	Cough	32	32	48	------
		Sputum production.	24	15	20	------
		Chest illness	5	4	5	------
Edwards, et al. (*55*).	1,737 male outpatients.	Chronic bronchitis	17	[1]19	31	14
Ashford, et al. (*4*).	4,014 male workers in 3 Scottish collieries.	Bronchitis	10	[1] 35	21	37
		Pneumoconiosis	11	[1] 34	14	2
Bower (*11*)	95 male bank employees.	Cough	0	0	29	------
		Sputum production.	8	15	33	------
		Wheeze	8	31	33	------
		Chest illness	15	54	40	------
Wynder, et al. (*114*).	315 male patients in New York and 315 male patients in California.	Cough (New York).	14	33	56	51
		Cough (California).	22	30	67	66
		Influenza (New York).	11	21	24	------
		Influenza (California).	28	24	31	------
		Chest illness (New York).	9	10	12	------
		Chest illness (California).	7	6	11	------
Densen, et al. (*24*).	5,287 male postal and 7,213 male transit workers in New York City.	Persistent cough	7	11	25	------
		Persistent sputum production.	11	16	26	------
		Dyspnea	16	19	26	------
		Wheeze	14	21	32	------
		Chest illness	13	16	18	------
Cederlof, et al. (*18*).	4,379 twin pairs, all U.S. veterans.	Cough	4	7	17	------
		Prolonged cough	2	4	11	------
		Bronchitis	2	3	10	------
Rimington (*76*).	41,729 male volunteers.	Chronic bronchitis	5	[1] 9	17	------

TABLE 34.—*Prevalence of respiratory symptoms and illness by type of smoking*—Continued

Author, reference	Number and type of population	Illness	Percent prevalence			
			Non-smoker	Total pipe and cigar	Cigarette only	Mixed
Comstock, et al. (*19*).	670 male telephone employees.	Persistent cough	10	16	41	------
		Persistent sputum.	13	20	42	------
		Dyspnea	33	39	44	------
		Chest illness in past 3 years.	14	18	20	------
Lefcoe and Wonnacott (*69*).	310 male physicians in London, Ontario.	Chronic respiratory disease.	9	18	44	------
		Chronic bronchitis	1	12	34	------
		Obstructive lung disease.	1	3	4	------
		Asthma	7	3	6	------
		Rhonchi	0	3	9	------

[1] Figures for pipe only.

TABLE 35.—*Pulmonary function values for cigar and pipe smokers as compared to nonsmokers*

Author, reference	Number and type of population	Function	Type of smoking			
			Non-smoker	Total pipe and cigar	Cigarette only	Mixed
Ashford, et al. (*4*).	4,014 male workers in 3 Scottish collieries.	$FEV_{1.0}$	3. 39	[1] 2. 59	3. 14	2. 62
Goldsmith, et al. (*57*).	3,311 active or retired longshoremen.	Puffmeter	313. 63	299. 26	303. 44	------
		$FEV_{1.0}$	2. 99	2. 80	2. 91	------
		TVC	3. 87	3. 68	3. 88	------
Comstock, et al. (*19*).	670 male telephone employees.	$FEV_{1.0}$	3. 12	3. 26	2. 82	------
Lefcoe and Wonnacott (*69*).	310 male physicians in London, Ontario.	$FEV_{1.0}$	3. 39	3. 17	3. 11	------
		MMFR liters per second.	4. 09	4. 17	3. 64	------

[1] Figures for pipe only.

Cigarette smokers have an increased prevalence of peptic ulcer disease and a greater peptic ulcer mortality ratio than is found in nonsmokers. These relationships are stronger for gastric ulcer than for duodenal ulcer. Cigarette smoking appears to reduce the effectiveness of standard peptic ulcer treatment regimens and slows the rate of ulcer healing. Cigar and pipe smokers experience higher death rates from peptic ulcer disease than nonsmokers. These rates are higher for gastric ulcers than for duodenal ulcers but are somewhat less than those rates experienced by cigarette smokers. Table 31 presents the mortality ratios for ulcer disease in cigar and pipe smokers as reported in the prospective epidemiological studies.

Retrospective or cross-sectional studies by Trowell (*95*), Allibone and Flint (*2*), Doll, et al. (*29*), and Edwards, et al. (*33*) contain data on ulcer disease in pipe smokers as well as cigarette smokers. No association was found between pipe smoking and ulcer disease in these investigations.

TABLE 36.—*Mortality ratios for peptic ulcer disease in male cigar and pipe smokers. Summary of prospective studies*

Author, reference	Illness	Type of smoking					
		Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Hammond and Horn (*40*).	Duodenal ulcer	1.00	0.25	1.67	------	2.16	------
Doll and Hill (*26, 27*).	Gastric ulcer	1.00	-----	-----	4.00	7.00	5.30
Hammond (*38*)	Gastric ulcer	1.00	-----	-----	2.04	2.95	------
	Duodenal ulcer	1.00	-----	-----	.92	2.86	------
Kahn (*50*)	Gastric ulcer	1.00	2.90	2.84	2.48	4.13	------
	Duodenal ulcer	1.00	1.58	1.59	1.39	2.98	------

Little Cigars

In the past year, several new brands of little cigars (weighing 3 pounds or less per 1,000) have appeared on the national market. These cigarette-sized products are manufactured, packaged, advertised, and sold in a manner similar to cigarettes. Little cigars enjoy several legal advantages over cigarettes: They have access to television advertising; they are taxed by the Federal Government and by most States, at much lower rates than cigarettes, resulting in a significant price advantage;

and they do not carry the warning label required on cigarette packages and in cigarette advertising. A market appears to be developing for these products, as there has recently been a sharp increase in the shipment of little cigars destined for domestic consumption (table 37).

It is important to estimate the potential public health impact of these little cigars. An adequate epidemiological evaluation of the effect of little cigar smoking on health could take 10 or 15 years and is probably an impractical consideration; however, a review of the epidemiological, autopsy, and experimental data concerning the health consequences of cigarette, pipe, and cigar smoking summarized in this and previous reports is helpful in considering the potential impact on health of smoking little cigars. An analysis of the chemical constituents suggests that both cigarettes and cigars contain similar compounds in similar concentrations. Two exceptions are reducing sugars, which are not found in quantity in the fermented tobaccos commonly used in cigars, and the pH of the inhaled smoke. The pH of the smoke from U.S. commercial cigarettes is below 6.2 from the first to the last puff, whereas the smoke from the last half of a cigar may reach as high as pH 8 to 9. With increasing pH, nicotine is increasingly present in the smoke as the free base. Skin painting experiments in mice indicate that tumor yields with cigar or pipe "tars" are nearly identical with those obtained with cigarettes "tars". In addition, the epidemiological data suggest that depth of inhalation probably accounts for the fact that cigarettes are so much more harmful than cigars and pipes in contributing to the development of lung cancer, coronary heart disease, and nonneoplastic respiratory disease. For such diseases as cancer of the oral cavity, larynx, and esophagus, where smoke from cigars, pipes, and cigarettes is available to the target organ at comparable levels, the mortality ratios are very similar for all three forms of tobacco use. Several factors, including "tar," nicotine, and the pH of the smoke, probably operate to influence inhalation patterns of smokers. The relative contribution of individual factors to the inhalability of a tobacco product has not been determined.

Smoking those brands of little cigars which can be inhaled by a significant portion of the population in a manner similar to the present use of cigarettes would probably result in an increased risk of developing those pulmonary and cardiovascular diseases which have been associated with cigarette smoking. On the other hand, smoking those little cigars which are used like most large cigars whereby the smoke is rarely inhaled would probably result in lower rates of those pulmonary and cardiovascular diseases than would be found among cigarette smokers.

Only a limited analysis is available comparing the chemical compounds found in little cigars, cigarettes, and large cigars. The FTC analyzed the tar and nicotine content of all the little cigars (*34*) and cigarettes (*97*) currently available on the market. Little cigars have

generally a higher "tar" and nicotine level than cigarettes, although considerable overlap results in some little cigar brands having "tar" and nicotine levels comparable to those of some brands of cigarettes (figs. 4 and 5). Hoffmann and Wynder (*44*) recently compared three brands of little cigars with an unfiltered cigarette, a filtered cigarette, and a large cigar. They measured a number of smoke constituents, including: "tar," nicotine, carbon monoxide, carbon dioxide, reducing sugars, hydrogen cyanide, acetaldehyde, acrolein, pyridines, phenols, benz(a)anthracene, and benzo(a)pyrene (table 32). Cigarette A was the Kentucky reference cigarette, cigarette B was a popular brand of filter cigarette. Cigar A was an 85 mm. little cigar, cigar B was an 85 mm. little cigar, cigar C was a 95 mm. small cigar, and cigar D was a 112 mm. popular brand of medium sized cigar.

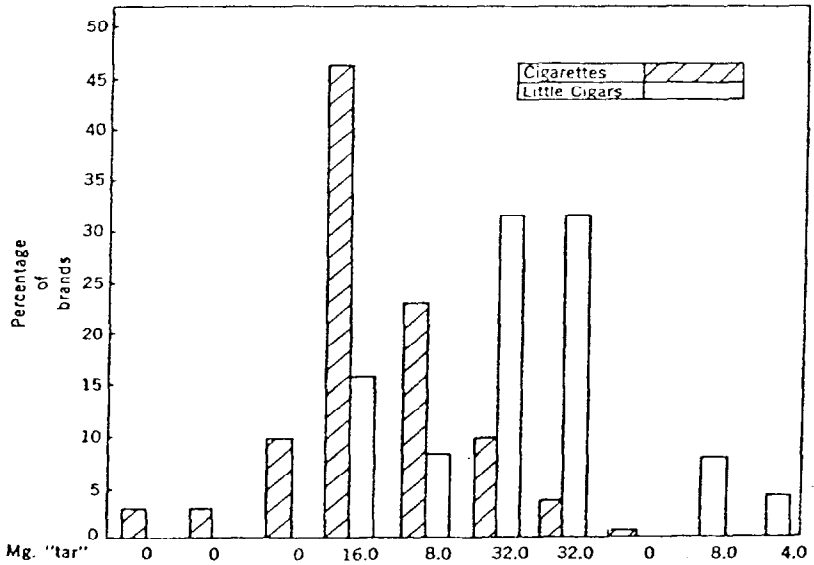
The smoke pH was analyzed puff by puff (table 39). Cigarette smoke was found to be acidic (pH less than 7) for the entire cigarette. The smoke from little cigars became alkaline only in the last puff or two, whereas about the last 40 percent of the puffs from the larger cigar were alkaline. Although the pH of the total condensate obtained from cigarettes is usually acidic and the total condensate obtained from cigars is usually alkaline, the above data indicate that smoke pH of tobacco products changes during the combustion process. Smoke from large cigars may be acidic during the first portion of the smoke and not become alkaline until the last half of the cigar is smoked.

Brunnemann and Hoffmann (*15*), using the same techniques described above, examined the effect of 60 leaf constituents on smoke pH. For several varieties of cigarette tobacco, they found a high correlation between the total aklaloid and nitrogen content and smoke pH. Stalk position also affected smoke pH. Tobacco leaves near the top of the plant, which contain high levels of tar and nicotine, yielded a smoke with a much higher pH than leaves lower on the plant. At present it is not known to what extent these factors influence the pH of the smoke of tobaccos commonly used in cigars or how these kinds of pH changes influence the inhalability of tobacco smoke.

The inhalation of smoke, however, appears to be the most important factor determining the impact a cigar will have on overall health. Those physical and chemical characteristics of a tobacco product which most influence inhalation of tobacco smoke have not been accurately determined. Nevertheless, it appears likely that the smoke of some brands of cigars may be compatible with inhalation by a significant portion of the smoking population, since: (*a*) Little cigars have tar and nicotine levels which, in some brands, are similar to the levels found in cigarettes, and (*b*) the pH of the smoke of some little cigar brands is acidic for the major portion of the little cigar and becomes alkaline only in the last puff or two.

It is reasonable to conclude that smoking little cigars may result in health effects similar to those associated with smoking cigarettes if little cigars are smoked in amounts and with patterns of inhalation similar to those used by cigarette smokers, for the reasons cited above, and these additional reasons: (*a*) In those little cigars for which preliminary data are available, the concentrations of carbon monoxide, hydrogen cyanide, acetaldehyde, acrolein, pyridine, phenol, and polycyclic hydrocarbon levels are comparable to those found in cigarettes; (*b*) cigarette smokers who switch to cigars appear to be more likely to inhale cigar smoke than cigar smokers who have always smoked cigars (*14*); and (*c*) cigarette smokers who switch to little cigars may be inclined to use them as they did cigarettes because of the physical similarities between the little cigars and cigarettes, including their size and shape, the number in a package, the burning rate, and the time it takes to smoke them.

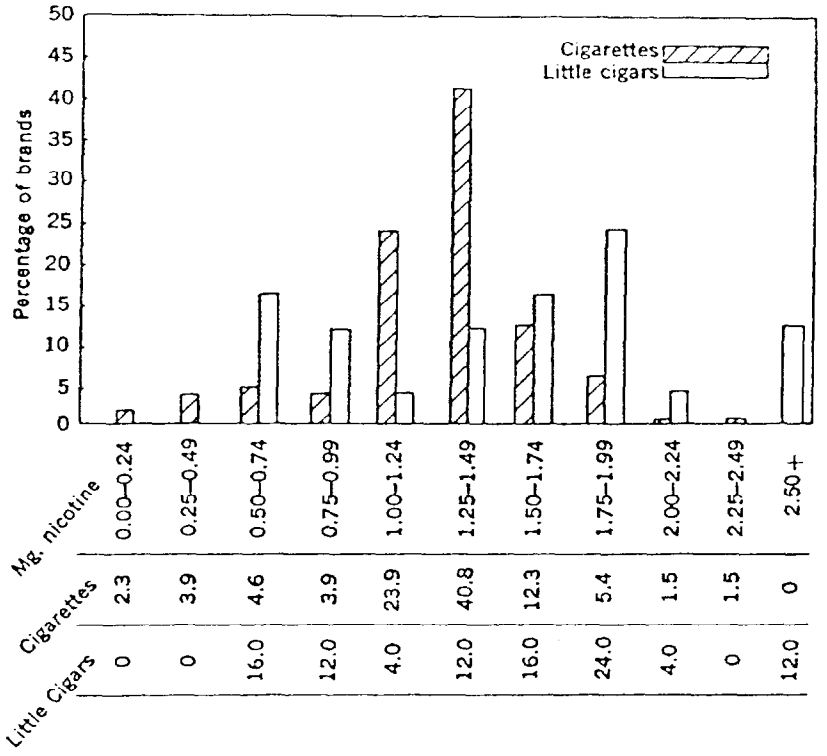
Figure 4.—Percent distribution of 130 brands of cigarettes and 25 brands of little cigars by "tar" content.



Mg. "tar"	0	0	0	16.0	8.0	32.0	32.0	0	8.0	4.0
Cigarettes	0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49
Little Cigars	3.1	3.1	10.0	46.2	23.1	10.0	3.9	0.8	0	0

SOURCE: U.S. Department of Health, Education, and Welfare (*97*) and Federal Trade Commission (*34*).

Figure 5.—Percent distribution of 130 brands of cigarettes and 25 brands of little cigars by nicotine content.



Mg. nicotine	0.00–0.24	0.25–0.49	0.50–0.74	0.75–0.99	1.00–1.24	1.25–1.49	1.50–1.74	1.75–1.99	2.00–2.24	2.25–2.49	2.50+
Cigarettes	2.3	3.9	4.6	3.9	23.9	40.8	12.3	5.4	1.5	1.5	0
Little Cigars	0	0	16.0	12.0	4.0	12.0	16.0	24.0	4.0	0	12.0

SOURCE: U.S. Department of Health, Education, and Welfare (97) and Federal Trade Commission (34).

TABLE 37.—*Shipment of small and large cigars destined for domestic consumption (1970, 1971, 1972)*

Year	1970	1971	1972
	Small cigars		
January	58, 328, 520	85, 753, 780	123, 477, 550
February	63, 431, 580	72, 092, 205	179, 817, 839
March	85, 881, 860	46, 542, 800	198, 165, 593
April	101, 613, 500	59, 059, 920	125, 335, 740
May	81, 093, 180	93, 237, 473	159, 334, 565
June	82, 471, 120	94, 560, 140	180, 582, 243
Subtotal	472, 819, 760	451, 246, 318	966, 713, 530
July	62, 143, 140	70, 332, 500	127, 713, 320
August	68, 220, 365	127, 709, 310	670, 936, 869
September	79, 101, 045	95, 027, 340	422, 534, 705
October	90, 752, 880	109, 567, 900	708, 116, 830
November	64, 290, 600	106, 666, 107	551, 326, 888
December	63, 806, 010	123, 809, 553	485, 587, 014
Subtotal	428, 314, 040	633, 112, 710	2, 966, 215, 626
Yearly total	901, 133, 800	1, 084, 359, 028	3, 932, 929, 156
	Large cigars		
January	581, 742, 001	573, 039, 120	534, 565, 488
February	595, 249, 522	586, 810, 844	562, 414, 577
March	629, 977, 375	665, 998, 099	654, 827, 796
April	652, 800, 200	655, 850, 213	554, 242, 048
May	748, 040, 796	670, 064, 933	719, 489, 529
June	644, 539, 031	692, 436, 529	578, 501, 068
Subtotal	3, 852, 348, 925	3, 844, 199, 738	3, 604, 040, 506
July	647, 397, 547	619, 838, 386	520, 873, 339
August	673, 082, 971	662, 970, 148	682, 331, 630
September	721, 561, 449	680, 476, 418	594, 843, 957
October	797, 601, 253	679, 420, 968	693, 150, 668
November	696, 526, 464	742, 948, 802	650, 746, 540
December	596, 244, 159	516, 879, 415	437, 429, 996
Subtotal	4, 132, 413, 843	3, 902, 534, 137	3, 579, 356, 130
Yearly total	8, 084, 762, 768	7, 746, 733, 875	7, 183, 396, 636

Source: U.S. Department of the Treasury (*101*).

TABLE 38.—*Selected compounds in mainstream smoke*

Smoke compound	Cigarette A (nonfilter)	Cigarette B (filter)	Little cigar A	Little cigar B	Small cigar C
"Tar", milligram per cigarette	36. 1	20. 3	17. 4	31. 8	40. 6
Nicotine, milligram per cigarette	2. 7	1. 4	. 6	1. 8	3. 1
Carbon monoxide, volume percent	4. 6	4. 5	5. 3	11. 1	7. 7
Carbon dioxide, volume percent	9. 4	9. 6	8. 5	13. 2	12. 7
Reducing sugars, percent of tobacco weight	9. 3	7. 9	1. 5	2. 9	2. 7
Hydrogen cyanide, microgram per cigarette	536. 0	361. 0	381. 0	697. 0	1, 029. 0
Acetaldehyde, microgram per cigarette	770. 0	774. 0	630. 0	1, 238. 0	1, 150. 0
Acrolein, microgram per cigarette	105. 0	71. 0	41. 0	54. 0	66. 0
Total pyridines, micrograms per cigarette	82. 8	27. 3	58. 0	85. 3	80. 3
Phenol, microgram per cigarette	124. 2	33. 0	35. 1	63. 4	94. 1
Benz(a)anthracene, nanogram per cigarette	74. 0	31. 0	34. 0	25. 0	39. 0
Benzo(a)pyrene, nanogram per cigarette	47. 0	20. 0	18. 0	22. 0	30. 0

Source: Hoffmann, D., Wynder, E. L. (44).

TABLE 39.—*The pH of the mainstream smoke of selected tobacco products*

[Numbers in parentheses indicate number of last puff.]

Average pH	Cigarette A (nonfilter)	Cigarette B (filter)	Little cigar A	Little cigar B	Small cigar C	Cigar D
3d puff	6. 19	6. 15	6. 44	6. 55	6. 53	6. 47
5th puff	6. 14	6. 12	6. 34	6. 46	6. 49	----------
7th puff	6. 09	6. 01	7. 03	6. 51	6. 56	----------
9th puff	6. 02	5. 83	----------	6. 98	6. 59	6. 27
13th puff	----------	----------	----------	----------	----------	6. 39
18th puff	----------	----------	----------	----------	----------	6. 41
23d puff	----------	----------	----------	----------	----------	6. 81
28th puff	----------	----------	----------	----------	----------	7. 22
33d puff	----------	----------	----------	----------	----------	7. 53
38th puff	----------	----------	----------	----------	----------	7. 78
Last puff	5. 96(11)	5. 76(10)	7. 73 (8)	7. 25(10)	7. 11(11)	7. 96(43)

Source: Hoffmann, D., Wynder, E. L. (44).

Conclusions

Pipe and cigar smokers in the United States as a group experience overall mortality rates that are slightly higher than those of nonsmokers, but these rates are substantially lower than those of cigarette smokers. This appears to be due to the fact that the total exposure to smoke that a pipe or cigar smoker receives from these products is relatively low. The typical cigar smoker smokes fewer than five cigars a day and the typical pipe smoker smokes less than 20 pipefuls a day. Most pipe and cigar smokers report that they do not inhale the smoke. Those who do inhale, inhale infrequently and only slightly. As a result, the harmful effects of cigar and pipe smoking appear to be largely limited to increased death rates from cancer at those sites which are exposed to the smoke of these products. Mortality rates from cancer of the oral cavity, intrinsic and extrinsic larynx, pharynx, and esophagus are approximately equal in users of cigars, pipes, and cigarettes. Inhalation is evidently not necessary to expose these sites to tobacco smoke. Although these are serious forms of cancer, they account for only about 5 percent of the cancer mortality among men.

Coronary heart disease, lung cancer, emphysema, chronic bronchitis, cancer of the pancreas, and cancer of the urinary bladder are diseases which are clearly associated with cigarette smoking, but for cigar and pipe smokers death rates from these diseases are not greatly elevated above the rates of nonsmokers. These diseases seem to depend on moderate to deep inhalation to bring the smoke into direct contact with the issue at risk or to allow certain constituents, such as carbon monoxide, to be systematically absorbed through the lungs or to affect the temporal patterns of absorption of other constituents such as nicotine that can be absorbed either through the oral mucosa or through the lungs. Evidence from countries where smokers tend to consume more cigars and inhale them to a greater degree than in the United States indicates that rates of lung cancer become elevated to levels approaching those of cigarette smokers.

Available data on the chemical constituents of cigar, pipe, and cigarette smoke suggest that there are marked similarities in the composition of these products. Pipe and cigar smoke, however, tends to be more alkaline than cigarette smoke, and fermented tobaccos commonly used in pipes and cigars contain less reducing sugars than the rapidly dried varieties commonly used in cigarettes.

Experimental evidence suggests that little difference exists between the tumorigenic activities of tars obtained from cigar or cigarette

tobaccos. Malignant skin tumors appear somewhat more rapidly and in larger numbers in animals whose skin has been painted with cigar tars than in those animals painted with cigarette tars.

One must conclude that some risk exists from smoking cigars and pipes as they are currently used in the United States, but for most diseases this is small compared to the risk of smoking cigarettes as they are commonly used. Nevertheless, changes in patterns of usage that would bring about increased exposure either through increased individual use of cigars and pipes or increased inhalation of pipe and cigar smoke have the potential of producing risks not unlike those now incurred by cigarette smokers. Mechanical or chemical modifications of pipe tobacco and cigars that would result in a smoke more compatible with inhalation could have this effect.

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Chapter 11

Exercise Performance

Source: 1973 Report, Chapter 7, pages 237 - 249.

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Introduction

Although it has long been held by athletes and coaches that cigarette smoking is associated with "shortness of wind" and impaired performance, until recently there has been little scientific evidence to support this view. In the past few years, a variety of studies have appeared dealing with the effect of cigarette smoking on the response of man to exercise. The following is a review of these studies.

Age, sex, training, health, weight, and other factors are known to influence exercise performance. Because most of the investigations were carried out in healthy, young male volunteers, the groups were quite comparable with regard to age, sex, and health; however, weight, training, and other factors were often inadequately controlled. Furthermore, problems in study design and statistical analysis limit the value of several of these studies.

Many forms of exercise were performed in these experiments, including: pedaling a bicycle ergometer, running on a treadmill, running on a track, swimming, step climbing, gripping a hand dynamometer, and doing several different exercise activities as part of a battery of tests. Small to maximum amounts of work were carried out in the various studies revewed.

Studies of Smokers

Most of the studies of habitual cigarette smokers followed a similar format with respect to smoking: (*a*) The subjects refrained from smoking for a few hours prior to testing, and (*b*) two test runs were performed, one without smoking and one in which smoking immediately preceded the exercise or was incorporated with the exercise protocol.

Several investigators (*1*, *15*, *28*) studied the effect of smoking on maximum grip strength. Willgoose (*28*) reported a greater mean percent recovery of grip strength after the nonsmoking trial than after the smoking trial. Kay and Karpovich (*15*) and Anderson and Brown (*1*) all followed a protocol similar to that of Willgoose except that they randomized the smoking and nonsmoking trials, and substituted

a "placebo" cigarette for the nonsmoking trial. In neither of these studies were statistically significant differences observed between the grip scores for the smoking and nonsmoking trials.

Reeves and Morehouse (*24*) administered a battery of tests to 15 colleges students. The tests were: A tapping test, a strength test. a jumping test, and the short form of the Harvard step test. No statistically significant differences in performance were noted under conditions of smoking or nonsmoking.

A total of 32 college students from intermediate swimming classes abstained from smoking for 15 minutes, 2 hours, and 12 hours in a study conducted by Pleasants, et al. (*23*). Following the abstinence, they swam distances of 100 and 200 yards. Although actual swimming times were not published, the authors reported no statistically significant differences between the mean swimming times after the different periods of abstinence for either distance.

In 1946, Juurup and Muido (*13*) carried out several experiments in which three young cigarette smokers exercised on a Krogh's bicycle ergometer. Smoking was found to increase the pulse rate at rest as well as during exercise. Although the effect was less consistent than on the heart rate, smoking was also associated with elevated blood pressure. Smoking had no effect on oxygen consumption. Henry and Fitzhenry (*12*), in 1949, using the bicycle ergometer, also found that smoking exerted no effect on oxygen consumption. In the same year, Karpovich and Hale (*14*) studied bicycle ergometer performance in eight young men. In all subjects, the average riding time was better in nonsmoking tests than in smoking tests; however, the results were statistically significant for only three of the eight subjects.

Kerrigan, et al. (*16*) more recently measured direct arterial blood pressure, heart rate, and cardiac output in 25 habitual smokers at rest and after exercise. Smoking two cigarettes produced statistically significant ($P<0.01$) increases in cardiac index, heart rate, and arterial mean pressure compared to the immediately preceding control period. Exercise after smoking resulted in an increase in cardiac index over either the resting period or the exercise period which followed abstinence; the resultant cardiac index appeared to be approximately the sum of the exercise and smoking effects. Exercise tests preceded by smoking were also associated wtih significantly higher ($P<0.01$) and more prolonged elevations of blood pressure than those not preceded by smoking.

In the study by Goldbarg, et al. (*11*) of nine habitual smokers performing submaximal exercise on a bicycle ergometer, cardiovascular responses were measured via pulmonary and subclavian artery catheters. At rest, after smoking, the mean cardiac index and mean heart rate increased. During successively increasing levels of exercise, the heart rate was greater and stroke index lower than values for

comparable work before smoking. The net effect of smoking was to decrease the effiicency of the heart during exercise in the upright position by causing a smaller stroke volume and a higher heart rate.

Rode and Shephard (*26*) investigated near maximal treadmill exercise performance in six habitual smokers. A 1-day abstinence from cigarette smoking was associated with a 13- to 79-percent decrease in the oxygen cost of breathing. Abstinence was also followed by a slowing of the heart rate and a decrease in expiratory minute volume after exercise.

The study of Krumholz, et al. (*18*) is different from those cited previously in that bicycle ergometer exercise performance was measured in habitual smokers both before and after 3 to 6 weeks of abstinence. Among the 10 subjects who abstained from smoking for 3 weeks, there was a statistically significant ($P<0.05$) decrease in heart rate, oxygen debt, and ratio of oxygen debt to total increase in oxygen uptake produced by the 5 minutes of exercise.

Using a "double 9-inch progressive step test" Rode and Shephard (*25*) studied several hundred participants of a smoking withdrawal clinic at the time of entry and at a 1-year followup. Among those who returned for the followup and who gave up smoking, absolute aerobic power increased insignificantly; however, the relative aerobic power diminished in both sexes among those who quit smoking because of the weight gain experienced.

Studies Comparing Smokers to Nonsmokers

Athletic Performance

In 1968 Cooper, et al. (*6*) evaluated 419 airmen during their initial 6 weeks on active duty in the USAF. A 12-minute maximum running test was performed at least 1 hour after cigarette smoking. The mean distance covered in 12 minutes by the nonsmokers was significantly greater ($P<0.05$) than that covered by the smokers at the beginning, the middle, and the end of training. All categories of smokers and nonsmokers improved their performance at the end of training; however, the maximum change in performance of those smoking 10 to 30 cigarettes per day was significantly ($P<0.001$) less than that of nonsmokers.

David (*7*) administered a battery of tests to 88 military personnel, aged 19 to 39 years. A 1-mile run was included in the testing, and cigarette smoking was associated with a significant decrease in performance in this event.

Some 45 special forces soldiers were investigated at sea level and 13,000 feet above sea level by Fine (*8*). The subjects were randomly assigned to a placebo group or an acetazolamide treated group. Cigarette smoking was positively correlated to decrements in 600-yard running performance from sea level to altitude in both groups.

Pleasants (*22*) studied 106 students from intermediate university swimming classes. Swimming times were measured for 100- and 200-yard distances before and after training and for 800-yard distances after training. The mean swimming times of nonsmokers were less than those of smokers in six of seven listed categories, but these differences were not statistically significant.

Bicycle Ergometer Performance

Chevalier, et al. (*5*) investigated cardiovascular parameters in 32 young physicians after a standard 5-minute ergometer test. Oxygen debt accumulation among smokers was significantly ($P<0.01$) greater than among nonsmokers. The heart rate at rest and 3 minutes after exercise was significantly ($P<0.02$) faster in smokers than in nonsmokers.

Using a 5-minute ergometer test, 18 housestaff physicians, half of whom smoked, were investigated by Krumholz, et al. (*17*). They noted the following: Oxygen debt accumulation after exercise was significantly ($P<0.02$) greater in smokers than non-smokers, the ratio of the oxygen debt to total increased oxygen uptake during exercise was significantly ($P<0.001$) greater in smokers than in nonsmokers, and the diffusing capacity at rest and with exercise was significantly ($P<0.05$) decreased in smokers compared to nonsmokers.

Kerrigan, et al. (*16*) studied cardiovascular parameters in smokers and nonsmokers at rest, during, and after a 5-minute bicycle ergometer ride. Cardiac index and blood pressure values obtained during exercise performed immediately after smoking were greater than those found in nonsmokers performing the same exercise. Similarly, heart rate and blood pressure remained elevated for longer periods in those who exercised immediately after smoking than in nonsmokers performing the same task.

Aerobic capacity scores were examined in 60 university student volunteers by Peterson and Kelley (*20*). Subjects worked at submaximal levels on a bicycle ergometer before, during, and after a training program. At all of these intervals, nonsmokers had significantly ($P<0.05$) higher mean aerobic capacity scores than smokers. Both groups increased their aerobic capacity during training but nonsmokers consistently performed better throughout training.

Treadmill Performance

In 1960 Blackburn, et al. (*4*) carried out several measurements of cardiovascular function after different amounts of treadmill exercise were performed by 233 professional men, 159 university students, and 414 railroad workers. The differences between the smokers and nonsmokers were of small magnitude. Basal oxygen consumption was slightly higher in smokers than in nonsmokers. Also, resting pulse rates were higher in smokers of most groups.

Cooper, et al. (*6*) studied 47 out of 419 airmen with treadmill testing. Cardiopulmonary indices measured on the treadmill, including maximum indices, were comparable in smokers and nonsmokers except for a significant ($P<0.01$) reduction in the maximum minute volume among the smokers.

A total of 277 prospective Canadian firemen performed the Balke-Ware test of work capacity in treadmill studies carried out by Glassford and Howell (*10*). The mean performance scores of nonsmokers were significantly ($P<0.01$) greater than those of smokers.

The effect of vitamin C supplementation on treadmill exercise performance was investigated in 40 male volunteers by Bailey, et al. (*3*). Significant differences in oxygen utilization and ventilatory function between smokers and nonsmokers were noted in only two of the 24 separate analyses of variance performed.

Maximal oxygen intake during treadmill exercise was examined by McDonough, et al. (*19*) in 86 healthy, middle-aged male volunteers. Cigarette smoking was one of six variables which together provided a multiple correlation coefficient of 0.73.

Performance in Other Tests of Fitness

When physical fitness tests were administered to 88 military personnel by David (*7*), cigarette smoking was found to be associated with a significant ($P<0.001$) decrease in performance in the dodge and jump test, and a significant ($P<0.02$) decrease in performance in the crawling test.

Using a step test, a breath holding test, and an ergometer test, Franks (*9*) examined 58 middle-aged men. Nonsmokers were able to hold their breath longer and had greater vital capacity residual after the step test than the smokers.

In 1971, Wysokinski (*29*) studied 200 young Polish soldiers using Letunov's test which included 20 knee-bending exercises, a fast run for 20 seconds, and a run for 3 minutes. Cigarette smoking was associated with a significant ($P<0.01$) reduction in the vital capacity and a

marked rise in the pulse rate at rest and after exercise. Intense exercise also caused a greater rise in the systolic blood pressure in smokers than in nonsmokers.

Discussion

Most of the studies in habitual cigarette smokers compared exercise performance in "smoking" and "nonsmoking" runs after only a few hours of abstinence. In some studies, smoking adversely affected performance (*11*, *13*, *14*, *16*, *18*, *26*, *28*), while in others it did not (*1*, *12*, *15*, *23*, *24*). Some of these apparently discrepant results are due to differences in methodology and in amounts and types of work performed. In all of the more recent studies of habitual smokers in which moderate to near maximal amounts of work were performed and sophisticated measurements of oxygen transport and cardiopulmonary function were made, impairment of function during smoking trials was found (*11*, *16*, *18*, *26*).

The data of Krumholz, et al. (*18*) also raise the question of whether residual effects of cigarette smoking influence "nonsmoking" trials performed after a few hours of abstinence; they found statistically significant decreases in heart rate and oxygen debt produced by exercise after 3 weeks of cessation.

The work of Rode and Shephard (*25*) suggests that physical fitness improves with cessation, but this improvement may be negated if the subject gains a substantial amount of weight after giving up smoking.

Several investigators compared exercise performance or postexercise cardiopulmonary function of smokers to nonsmokers. Although only minor differences between smokers and nonsmokers were found in a few of these studies (*3*, *4*, *22*), in most of them (*5*, *6*, *7*, *8*, *10*, *16*, *17*, *20*, *29*) the performance or function of the nonsmokers was better than that of the smokers. Both nonsmokers and smokers improved their performance with training, but nonsmokers maintained their advantage throughout training (*6*, *20*).

Biomechanisms

The cited studies indicate that cigarette smoking exerts its adverse effect on exercise performance through several mechanisms. Cigarette smoking appears to impair cardiac performance during exercise by increasing the heart rate and exerting a variable effect on cardiac

output (*5, 11, 13, 16, 18, 26, 29*). Cigarette smoking is associated with an increased oxygen debt after exercise (*5, 18*). Also, one study indicated that the oxygen cost of hyperventilation was greater among smokers than among nonsmokers (*26*).

Some of these adverse effects of smoking on oxidative metabolism are mediated by the elevated carboxyhemoglobin levels found in smokers. CO exerts these effects through one or more of the following mechanisms: (*a*) Reduction of the amount of hemoglobin available for oxygen transport, (*b*) shift of the oxygen-hemoglobin dissociation curve to the left with consequent interference in oxygen release at the tissue level, (*c*) induction of arterial hypoxemia, and (*d*) possible interference with the homeostatic mechanism by which 2,3,DPG controls the affinity of hemoglobin for oxygen (*27*). Because carboxyhemoglobin has a half life in the body of at least 3 to 4 hours, its influence may still be measurable several hours after abstinence from smoking (*27*).

A recent investigation of maximal muscular exercise during CO intoxication in five male volunteers demonstrated reduced maximal O_2 consumption in spite of a much higher heart rate and a relative hyperventilation (*21*).

Astrand and Rodahl (*2*) commented recently on the adverse effect of cigarette smoking on oxygen transport: "All other factors being equal, a reduction in the oxygen-transporting capacity is associated with a corresponding reduction in physical performance capacity during heavy or maximal work * * *. Because a regular physical training program only increases the maximal oxygen uptake by some 10 to 20 percent, a 5- to 10-percent reduction in maximal aerobic power due to smoking may play a significant role in many types of athletic events and in very heavy work."

Other studies cited in this review document the adverse effect of smoking on pulmonary diffusing capacity (*18*) and on pulmonary function with exercise (*6, 29*).

Summary

Clinical studies in healthy, young men have shown that cigarette smoking impairs exercise performance, especially for many types of athletic events and activities involving maximal work capacity. Some of these effects are mediated by reduced oxygen transport and reduced cardiac and pulmonary function.

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Chapter 12

Harmful Constituents of Cigarette Smoke

Source: 1972 Report, Chapter 9, pages 137 - 150.

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HARMFUL CONSTITUENTS OF CIGARETTE SMOKE*

Cigarette smoke contains a large number and a wide variety of compounds which may result in complex and multiple pathophysiological effects on various tissues and organ systems. Although the constituents of cigarette smoke are usually divided for convenience into the two categories of particulate and gas phases,** many of them exist in a distribution equilibrium, that is, they are present partially in the gas phase and partially in the particulate phase. This review concerns itself with judgments concerning the harmful constituents of cigarette smoke whether these are found primarily in the gas phase or in the particulate phase.

Constituents of cigarette smoke may enter the body by a variety of routes. Theoretically, the route of entry and subsequent absorption could affect the degree to which various organs are subjected to specific cigarette smoke constituents. Some constituents, particularly the water soluble components of the gas phase, may be absorbed by the nasal and oropharyngeal mucous membranes, or may be dissolved in the saliva and swallowed, thus allowing for possible gastric or intestinal absorption. Other constituents are absorbed along the tracheobronchial tree, and the distance which they reach before being absorbed or deposited depends on such factors as the depth of inhalation and the particle size. The absorption of gases in the tracheobronchial tree appears to be in part dependent on the adsorption of gases to particulate matter. Another factor affecting the route and degree of absorption is the adequacy of pulmonary clearance by which constituents deposited or dissolved in the mucous sheath are delivered to the pharynx and then usually swallowed.

Of the hundreds of compounds identified in cigarette smoke, some occur in the smoke in concentrations which may be considered sufficient to present hazards to health. Other compounds appear in

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* This report attempts to summarize the areas of general consensus reached in a special one-day conference of experts in this field which met in June 1970. This is not to imply that there was unanimous agreement on all statements contained herein. A list of participants in the meeting appears in the Acknowledgments.

** It should be noted that there is, at present, no available instrumentation permitting the separation and individual collection of the particulate and gas phases which duplicates the precise physicochemical conditions prevailing in cigarette smoke as it is inhaled. A widely accepted arbitrary distinction between the two phases is as follows: If 50 percent or more of a given constituent is retained on a Cambridge filter (CM-113) during standardized machine smoking of a cigarette, then the compound is considered to belong to the particulate phase; if on the other hand more than 50 percent of the compound passes through the Cambridge filter under these conditions, then the constituent is considered to belong to the gas phase.

borderline concentrations. Still others, although potentially harmful, are probably not present in sufficient concentrations to contribute to the hazard, and some may be hazardous only when they interact with other substances in the smoke.

Substances and classes of substances in cigarette smoke which have been judged to contribute to the hazard of cigarette smoking have been classified into three priority groups. Those compounds which are judged most likely to contribute to the health hazards of smoking are listed in table 1. Additional substances which probably contribute to the health hazards of smoking are listed in table 2. Those compounds which are suspected contributors to the health hazards of smoking in the concentrations in which they are present in tobacco smoke are listed in table 3. Many other constituents of tobacco smoke are considered to be toxic under some conditions but probably do not present a health hazard in the concentrations in which they are generally found in cigarette smoke; these are not listed. This listing is not presented as final, and may be subject to modification as more information becomes available.*

In 1966, the Public Health Service prepared a technical report on "tar" and nicotine (*60*). Tobacco "tar" is the name given to the aggregate of particulate matter in cigarette smoke after subtracting nicotine and moisture. In that report it was stated:

> "It is clear that the overall risk associated with cigarette smoking increases as the average number of cigarettes consumed per day increases. In the studies which have reported other measures of exposure such as pack-years, degree of inhalation, and maximum level of cigarette consumption, the same type of relationship holds."

Individuals may differ in their inherent susceptibility to diseases in which cigarette smoking plays a role and differ in their exposure to other factors which may increase the likelihood of these diseases. Within these groups of varying risk, the degree of exposure to cigarette smoke appears to be the most critical factor for the development of smoking related disease. Therefore, the general statement that the lower the dosage the lower the risk is the most useful guide available. It was also stated that:

> "It is possible for a cigarette to be altered in such a way that its 'tar' and nicotine content is reduced but certain other harmful effects, for example the effect of the gaseous phase, may be increased. Although this is a theoretical possibility,

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* Subsequent to the conference on which this report was based, several studies were published reporting the presence of N-nitrosamines in cigarette smoke. Since these substances are accepted as carcinogens in experimental animals, they represent another portion of the "tar" which probably contributes to the total health hazard (18, 24).

there is no evidence that this has occurred to any serious degree."

The consensus is that there is inadequate evidence to support a change in that view at the present time.

In addition, it was concluded that "the preponderance of scientific evidence strongly suggests that the lower the 'tar' and nicotine content of cigarette smoke, the less harmful would be the effect." Several studies reported since that time have added strong support to this position. The present review is an attempt to identify those constituents of the "tar" as well as those constituents considered part of the gas phase which are most likely to contribute to the health hazards from cigarette smoking.

TABLE 1.—*Compounds in cigarette smoke judged most likely to contribute to the health hazards of smoking.*

Compound	Concentration in cigarette smoke micrograms/cigarette	Primary phase classification G—gas P—particulate	References
Carbon Monoxide	5,240–21,400	G	(1, 10, 23, 26, 29, 34, 35, 37, 42, 46, 49, 61, 63)
Nicotine	200–2,400	P	(9)
[1] "Tar"	3,000–33,000	P	(9)

[1] "Tar" is defined as the total particulate matter collected by a Cambridge filter (CM-113) after subtracting moisture and nicotine and includes the class of compounds known as polycyclic aromatic hydrocarbons (PAH). PAH are generally accepted as being responsible for a substantial portion of the carcinogenic activity of the total "tar." Although "tar" from different cigarettes varies in its carcinogenic potential as measured by the bioassay methods in current use, it remains the most practical single "indicator" of total carcinogenic potential. Special mention should be made of Beta Naphthylamine which is a known human urinary bladder carcinogen for which there is no known safe level of exposure and which has been reported present in tobacco smoke in very low concentrations (16, 28, 30) (0.022 μgm./cigarette).

It is recognized that the substances in cigarette smoke may interact so that the combined pathological effects of several substances may be quite different from the sum of their effects produced in isolation. An example of this type of interaction might be the carcinogenic effects of tobacco "tar" as a result of the combined action of cancer initiating, cancer promoting, and cancer accelerating agents in producing the total effect. Such interactions theoretically could take place among substances within the gas phase, or substances within the particulate phase, or between constituents of the gas phase and constituents of the particulate phase. In the absence of data which identify the interactions of cigarette smoke components, judgments concerning the action or identification of harmful substances in cigarette smoke have, of necessity, been made pri-

TABLE 2.—*Compounds in cigarette smoke judged as probable contributors to the health hazards of smoking.*

Compound	Concentration in cigarette smoke micrograms/cigarette	Primary phase classification G—gas P—particulate	References
Acrolein	45–140	G	(12, 20, 21, 27, 36, 43, 45)
Cresol (all isomers)	68–97	P	(20, 40)
Hydrocyanic Acid	100–400	G	(26, 38, 43, 45, 46, 49, 53)
Nitric Oxide	0–600	G	(1, 3, 15, 40, 42, 44, 57)
Nitrogen Dioxide	0–10	G	(1, 40, 44, 57)
Phenol	9–202	P	(7, 19, 20, 32, 50, 52)

marily on the basis of the action of the individual substances. Nevertheless, experimental evaluation of modified cigarette smoke should be designed to take into account the possibility of such interaction.

Until there is a better understanding of the relative importance of the interaction of the constituents of cigarette smoke in the development of the diseases associated with cigarette smoking, it will be difficult to assess the significance of the reduction or elimination of one or several of the constituents named in this report. However, it is reasonable to take the position that unless there is positive information to the contrary, cigarettes in which overall "tar" and nicotine levels have been reduced present to the smoker lower concentrations of the harmful substances in the particulate phase. If, at the same time, significant reductions are made in those gas phase constituents which also contribute to the hazards of smoking, the resulting product should be less hazardous to health.*

The consensus is that a progressive and simultaneous reduction of all substances considered likely to be involved in the health hazards of smoking should be encouraged as the most promising step available at the present time towards the development of a less hazardous cigarette. Primary emphasis should be given to the reduction of the three substances or classes of substances named in the first table, and as a second priority to the reduction of those substances or classes of substances in the second table before reducing

* An alternative point of view held by some is that smoking behavior is a response to the need to reach a certain nicotine level and that lowering the amount of nicotine available from a cigarette may result in an increase in the number of cigarettes smoked, the depth of inhalation, or the number of puffs in order to maintain an accustomed level. Such an increase in smoking might result in an increased inhalation of other hazardous substances in the smoke, thereby potentially negating the effect of reducing the amount available in each cigarette.

TABLE 3.—*Compounds in cigarette smoke judged as suspected contributors to the health hazards of smoking.*

Compound	Concentration in cigarette smoke micrograms/cigarette	Primary phase classification G—gas P—particulate	References
Acetaldehyde	180–1,440	G	(4, 21, 27, 36, 43, 45, 48, 49, 53, 59)
Acetone	88–650	G	(12, 21, 27, 36, 43, 45, 48, 49, 53)
Acetonitrile	140–200	G	(12, 43)
Acrylonitrile	10–15	G	(12, 43)
Ammonia	60–330	G	(2, 22, 40, 41, 43, 64)
Benzene	12–100	G	(11, 12, 25, 43, 45, 49, 53)
2,3–Butadione	43–200	G	(43, 46, 49, 53)
Butylamine	3	P	(31, 40, 41)
[1] Carbon Dioxide	23,100–78,300	G	(1, 10, 15, 23, 26, 29, 34, 35, 42, 46, 49, 63)
Crotononitrile	4	G	(43)
Dimethylamine	10–11	P	(31, 40, 41)
DDT	0–0.77	P	(17, 39, 54)
Endrin	0.06	P	(14)
Ethylamine	10–11	G	(22, 31, 40, 41)
Formaldehyde	20–41	G	(4, 36, 43, 48, 53)
Furfural	45–110	P	(4, 13, 36)
Hydrogen Sulphide	12–35	G	(10, 43, 51, 58)
Hydroquinone	83	P	(6, 7)
Methacrolein	9–11	G	(12, 43)
Methyl Alcohol	90–300	G	(12, 21, 43, 46, 49)
Methylamine	20–22	G	(22, 31, 40, 41)
Nickel compounds	0–0.58	P	(5, 8, 47, 55, 56)
Pyridine	25–218	P	(40, 62)

[1] CO_2 is included because of the hazard it may represent to those with CO_2 retention, such as those with advanced COPD.

those named in the third table. In addition to the epidemiological and pathological data gained from human studies, it is important to develop better bioassay systems to evaluate cigarettes modified by these general guidelines.

It should again be emphasized that, in addition to the variation in chemical properties of the cigarette being smoked, procedures within the control of the individual smoker such as how many cigarettes he smokes, how far down he smokes the cigarette, and how frequently and deeply he inhales are critical factors in determining how much of the harmful substances which can be produced by the burning cigarette is given the opportunity to injure him.

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