The Health Consequences of Smoking

A Report of the Surgeon General: 1971

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Preface

This report is a comprehensive review of more than 20 years of research into the problem of smoking and health. This research has been carried on under the sponsorship of many groups in this country and abroad, including governments, universities, private research institutions, voluntary health agencies, and the tobacco industry.

Seven years ago, an advisory committee to the Surgeon General concluded that cigarette smoking is a serious hazard to health and is related to illness and death from lung cancer, chronic bronchopulmonary disease, cardiovascular disease and other diseases. In the intervening years, a great deal of new research has been completed. This has resulted in a growing understanding of the biomechanisms whereby cigarette smoking adversely affects the human organism and contributes to the development of serious illness.

It is encouraging that cigarette consumption in this country is declining. If this decline can be maintained, it will result in better health for our population and in fewer deaths among those of our citizens who are in their most productive years of life.

JESSE L. STEINFELD, M.D.,
Surgeon General.

Acknowledgments

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CHAPTER 1

General Considerations, Preparation of the Present Document, and Summary of the Report

GENERAL CONSIDERATIONS

The first major development in the modern history of the effects of smoking on health occurred in 1950 with the publication of four retrospective studies on smoking habits among lung cancer patients and among controls (*1, 4, 6, 7*). At that time, the question was, "Are smokers more likely to get lung cancer than nonsmokers?" Although some epidemiologists were satisfied that the answer was in the affirmative, others turned for confirmation to prospective studies in which the smoking habits of large populations were recorded and the populations followed to identify subsequent mortality. The first report of Hammond and Horn in 1954 (*2*), showed significantly elevated overall death rates for smokers as compared to nonsmokers. This elevation in death rates, almost entirely confined to those who smoked cigarettes, together with the evidence for a gradient according to the amount smoked, changed the question from one concerning only lung cancer to one concerning overall death rates and from one concerning smoking to one primarily concerned with cigarette smoking. In effect, the question became, "Do cigarette smokers have higher overall death rates than nonsmokers and smokers of pipes and cigars?"

With the publication of the later reports of the major prospective studies in the late 1950's and early 1960's, it became clear that cigarette smokers had higher overall death rates than nonsmokers, as well as higher death rates from a number of individual causes of death. The question then became, "Why?"

When the Advisory Committee on Smoking and Health to the Surgeon General was established in 1962, it undertook the evaluation of the scientific evidence up to that time. The conclusion of the Committee in its 1964 Report was that: "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action." Not only did the Committee conclude that the evidence clearly showed that male cigarette smokers do in fact have higher death rates than nonsmokers but that the convergence of epidemiological, experimental, and pathological evidence also clearly indicated a cause-and-effect relationship for several of the implicated diseases, particularly cancer of the lung and chronic bronchitis. In several other important diseases, the evidence on biomechanisms to explain epidemiological

associations was felt to be inadequate at that time to draw firm conclusions about a cause-and-effect relationship.

Three and one-half years later, when The Health Consequences of Smoking: A Public Health Service Review, 1967 was published, the conclusions of the 1964 review were taken as a starting point, and the nature of the task of interpreting the scientific evidence was restated as follows:

1. How much mortality and excess disability are associated with smoking?
2. How much of this early mortality and excess disability would not have occurred if people had not taken up cigarette smoking?
3. How much of this early mortality and excess disability could be averted by the cessation or reduction of cigarette smoking?
4. What are the biomechanisms whereby these effects take place and what are the critical factors in these mechanisms?

That and subsequent reviews in 1968 and 1969 have provided some answers to these questions, particularly in summarizing the evidence for various theories as to how cigarette smoking affects the human organism to produce elevated disease and death rates.

At least five different processes have been suggested whereby cigarette smokers experience higher mortality or morbidity rates than do nonsmokers.

1. Cigarette smoking initiates a disease process by producing progressive irreversible damage. In this case, the total effect would be approximately proportional to the total accumulated dosage experienced over the years. Cessation of smoking leaves impaired function which does not improve appreciably but does not continue to deteriorate from continued exposure to cigarette smoke. However, such function may deteriorate through aging or through exposure to other harmful agents. It appears that such a relationship probably exists for chronic obstructive lung disease and possibly for the development of atherosclerotic heart disease.

2. Cigarette smoking initiates a disease process with continual repair and recovery until some critical point is reached at which the process is no longer reversible. The total effect would therefore be affected to some extent by accumulated exposure but would be affected also by the level of contemporary smoking. Cessation of smoking would result in a rapid reduction of risk provided the critical level initiating an irreversible process has not been reached. The evidence supports this kind of mechanism accounting both for the high dose-response relationship in lung cancer and for the reduction in risk from lung cancer among ex-smokers.

3. Cigarette smoking promotes a disease process either by providing positive support to the development of a pathological condition or by interfering with and diminishing the normal capa-

bility of the organism to cope with and defend against a disease process. This may take place by promoting the development of a subclinical disease to a clinically recognizable one, by promoting a mild disease state to a more severe form, or by increasing fatality rates of severe disease states. This type of mechanism could account for modestly increased mortality rates for a number of severe diseases for which there is no evidence that cigarette smoking itself has a role in initiating the disease. Some of the excess mortality from infectious respiratory disease and from coronary heart disease might take place through this kind of mechanism.

4. Cigarette smoking produces a set of temporary conditions which increase the probability that a critical event will occur with attendant disability and possibly fatal consequences. For example, there is evidence to support the theory that each cigarette can produce a set of conditions which increase the probability of myocardial damage through increased demand for oxygen at a time when the suppy is diminished. Presumably, once the supply/demand imbalance is alleviated, the probability of myocardial damage would revert to its normal level. Cessation of smoking should have an almost immediate effect of reducing the risk sharply for morbidity or mortality produced through this mechanism.

5. Cigarette smoking may be artificially related to excess disability or death by way of a close association with some other condition or exposure which is found at a high level in smokers, but not in nonsmokers, and is itself responsible for the disease. The one cause of death for which cigarette smokers have elevated death rates that is generally interpreted in this way is cirrhosis of the liver. Since most heavy consumers of alcoholic beverages are smokers, and since alcohol consumption is an important part of the process that produces cirrhosis of the liver, the high rate of cirrhosis among cigarette smokers is discounted as resulting from this kind of artificial relationship. Some authors have proposed that there may be genetic factors that link smoking and certain diseases in this fashion. Obviously, the cessation of smoking would have no effect on morbidity or mortality from diseases which are artificially related to smoking.

These different ways in which cigarette smoking can be related to elevated morbidity and mortality rates are important considerations in attempting to estimate the potential public health benefits of giving up smoking. For some types of relationship, there would be no benefits; for some, rather small benefits; for some, substantial benefits, taking place over a long period of time; and for others, substantial benefits taking place rather rapidly.

During the past few years, a sharp reduction has taken place in the cigarette smoking habits of the U.S. population. The Na-

tional Center for Health Statistics has recently published a comparison of smoking habits in the U.S. in 1955 and 1966 based on two large scale household surveys (*5*). These showed a drop in cigarette consumption in men under 55 years of age but no appreciable change among those 55 or over. Among women, every age group showed an increase in the eleven year period. A recent survey conducted for the National Clearinghouse for Smoking and Health, based on a much smaller sample (approximately 5,000 interviews), was conducted in the Spring of 1970 (*3*) (table 1). Even with the smaller number of cases, it is clear that a much larger drop took place in the four years from 1966 to 1970 than in the eleven years from 1955 to 1966. The drop extended to the age group 55–64 among men, again with no appreciable drop among men over age 65. For the first time, the increase in smoking among women leveled off, or even dropped slightly among women under 55. The increase among women over 55 was of a lesser magnitude than previously observed.

TABLE 1.—*Percentage of Current Smokers of Cigarettes (regularly or occasionally) by sex and age. U.S. Surveys: 1955 and 1966 (CPS-Current Population Surveys) and 1970 (NCSH-Survey conducted for National Clearinghouse for Smoking & Health).*[1]

	Male			Female		
Age	CPS 1955	CPS 1966	NCSH 1970	CPS 1955	CPS 1966	NCSH 1970
18–24	53.0	48.3	[2]47.0	33.3	34.7	[2]31.1
25–34	63.6	58.9	46.8	39.2	43.2	40.3
35–44	62.1	57.0	48.6	35.4	41.1	39.0
45–54	58.0	53.1	43.1	25.7	37.3	36.0
55–64	45.8	46.2	37.4	13.4	23.0	24.3
65 +	25.8	24.6	23.7	4.7	8.1	11.8

[1] 1955 survey based on approximately 45,000 persons; 1966 survey based on approximately 35,000 persons; 1970 survey based on approximately 5,000 persons.
[2] Estimated.

With the massive changes in smoking behavior which have taken place among adults in the past few years, largely as an expression of the desire to protect health, changes should be expected in mortality rates among those groups which have experienced the greatest reduction both in accumulated dosage and in concurrent dosage. An analysis of U.S. mortality rates for 1970 and the years to follow will provide a very valuable addition to the knowledge concerning the effects of smoking on death rates.

PREPARATION OF THE PRESENT DOCUMENT

Following the publication of Smoking and Health—Report of the Advisory Committee to the Surgeon General—in 1964, the fol-

lowing documents were published as reviews of the medical literature concerning the health consequences of smoking, as called for by Public Law 89–92:

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.

These documents reviewed the medical literature which had been published since the original Surgeon General's Report. This format of publishing a supplement to a supplement has become unwieldy, particularly in the light of the lack of availability of the previous reviews to the general public. Therefore, when Public Law 91–222 was signed into law on April 1, 1970 calling for an eighteen month interval between the last report and the new report, the decision was made to review the entire field with emphasis on the most recent additions to the literature.

The National Clearinghouse for Smoking and Health has the responsibility for continuous monitoring and compilation of the medical literature on the health consequences of smoking. This is accomplished through several mechanisms:

1. A scientific review corporation is on contract to extract articles on smoking and health from the medical and scientific literature of the world. This organization provides a semi-weekly accessions list with abstracts and copies of the various articles. Translations are called for as needed. Articles of pertinence are identified by a series of code words and phrases.

2. The National Library of Medicine, through the Medlars system, sends the National Clearinghouse for Smoking and Health a monthly listing of articles in the smoking and health area. These are reviewed, and pertinent articles are ordered.

3. Staff members keep up with the current contents of medical and scientific literature and identify articles of pertinence.

Initial drafts of the present review were prepared by Clearinghouse staff and consultants who reviewed the previous reports and identified those articles which have been important in the development of knowledge in this field. These were abstracted and placed into tabular form, and a draft text of the report was prepared. The first drafts of the individual chapters were sent to experts for review, criticism, and comment with respect to the articles reviewed, those articles not included, and conclusions. The drafts were then revised on the basis of these comments and rewritten until they met with general approval of the reviewers. The final

drafts were reviewed as a whole by the Director of the National Clearinghouse for Smoking and Health, the Director of the National Cancer Institute, the Director of the National Heart and Lung Institute, the Director of the National Institute of Environmental Health Sciences, and by six additional experts both within and outside of the Public Health Service.

SUMMARY OF THE REPORT

CARDIOVASCULAR DISEASES

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 smoking of pipes and cigars is appreciably less than that incurred by cigarette smokers.

2. Analysis of other factors associated with CHD (high serum cholesterol, high blood pressure, and physical inactivity) show 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 the 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 mon-

oxide, 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.

Summary Statement of Recent Additions to Knowledge Relating Smoking and Coronary Heart Disease.—A number of epidemiologic studies have provided additional evidence concerning cigarette smoking as a significant risk factor in the development of CHD. Experimental studies on animals have suggested that cigarette smoking, particularly the absorbed nicotine and carbon monoxide, contributes to the development of atherosclerosis.

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.

Nonsyphilitic 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.

Chronic Obstructive Bronchopulmonary Disease

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 pro-

duction, and breathlessness, when compared with nonsmokers. Ventilatory function is decreased in smokers when compared with nonsmokers.

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

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

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

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

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

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

8. Pathological studies have shown that cigarette smokers who die of diseases other than COPD have histologic changes characteristic of COPD in the bronchial tree and pulmonary parenchyma more frequently than do nonsmokers.

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

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

Summary Statement of Recent Additions of Knowledge Relating to Chronic Obstructive Bronchopulmonary Disease.—Studies have demonstrated that cigarette smokers show increased symptoms and pulmonary dysfunction as well as mortality from COPD when compared to nonsmokers. Investigations of alpha$_1$-antitrypsin deficiency in relationship to pulmonary emphysema have sug-

gested that cigarette smoking may act jointly with hereditary factors in the pathogenesis of pulmonary emphysema. A pathological study on animals has shown that long-term inhalation of cigarette smoke produces lesions characteristic of pulmonary emphysema.

CANCER

Lung Cancer·

1. Epidemiological evidence derived from a number of prospective and retrospective studies, coupled with experimental and pathological evidence, confirms 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 the 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 attributable to differences in exposures: 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 2 years.

Cancer of the Larynx

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.

Oral Cancer

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

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 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 that alcohol consumption may interact with cigarette smoking. This com-

bination of exposures is associated with especially high rates of cancer of the esophagus.

Cancer of the Urinary Bladder and Kidney

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 thereby to the development of urinary tract cancer.

Cancer of the Pancreas

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.

Summary Statement of Recent Additions of Knowledge Relating Smoking and Cancer.—Epidemiological studies have confirmed that cigarette smokers incur an increased risk of dying from lung cancer and that those smokers who switched to filter cigarettes incur a lesser risk. Pathological studies have shown that cancer of the lung and cancer of the larynx have been found in animals exposed to the long-term inhalation of cigarette smoke.

Smoking and Pregnancy

Maternal smoking during pregnancy exerts a retarding influence on fetal growth as manifested by decreased infant birthweight and an increased incidence of prematurity, defined by weight alone. There is strong evidence to support the view that smoking mothers have a significantly greater number of unsuccessful pregnancies due to stillbirth and neonatal death as compared to nonsmoking mothers. There is insufficient evidence to support a comparable statement for abortions. The recently published Second Report of the 1958 British Perinatal Mortality Survey, a carefully designed and controlled prospective study involving large numbers of patients, adds further support to the conclusions.

Peptic Ulcer

Cigarette smoking males have an increased prevalence of peptic ulcer disease and a greater peptic ulcer mortality ratio. These relationships are stronger for gastric ulcer than for duodenal ulcer. Smoking appears to reduce the effectiveness of standard peptic ulcer treatment and to slow the rate of ulcer healing.

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 2

Cardiovascular Diseases

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(A indicates tales located in Appendix at end of Chapter)

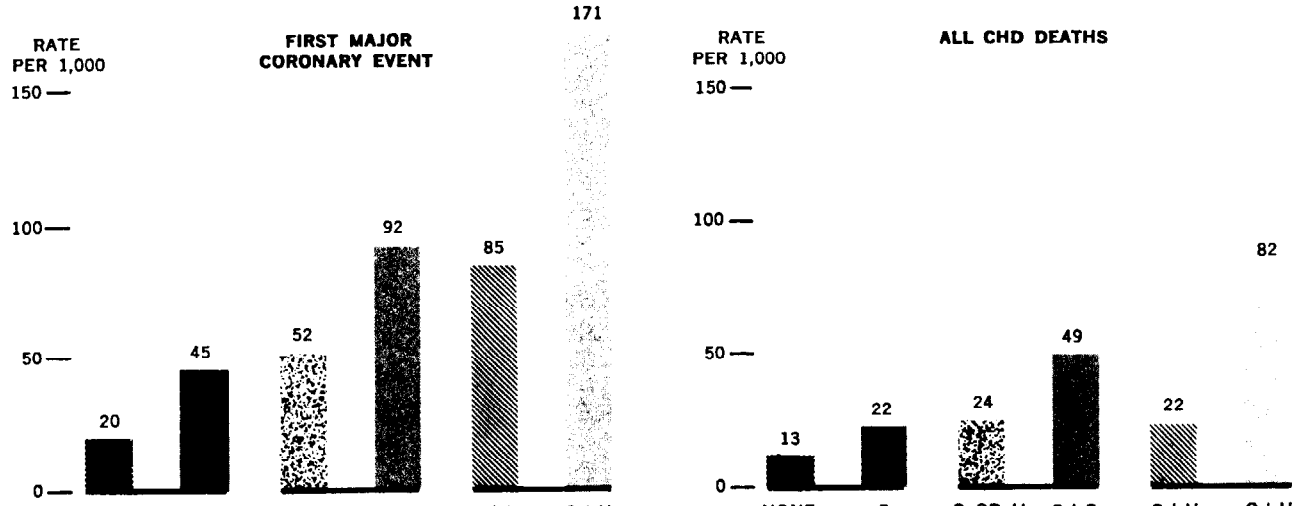
INTRODUCTION

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



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 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.

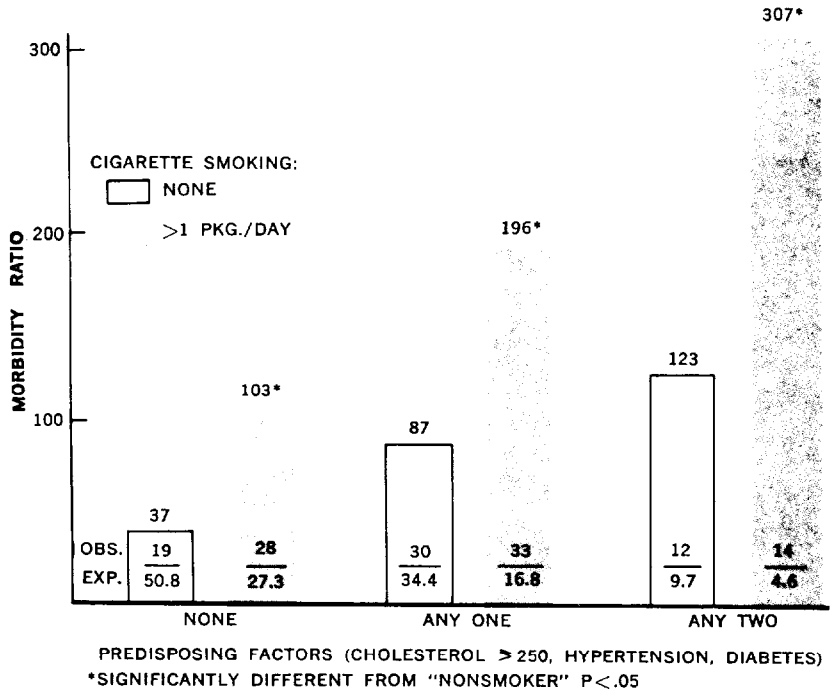
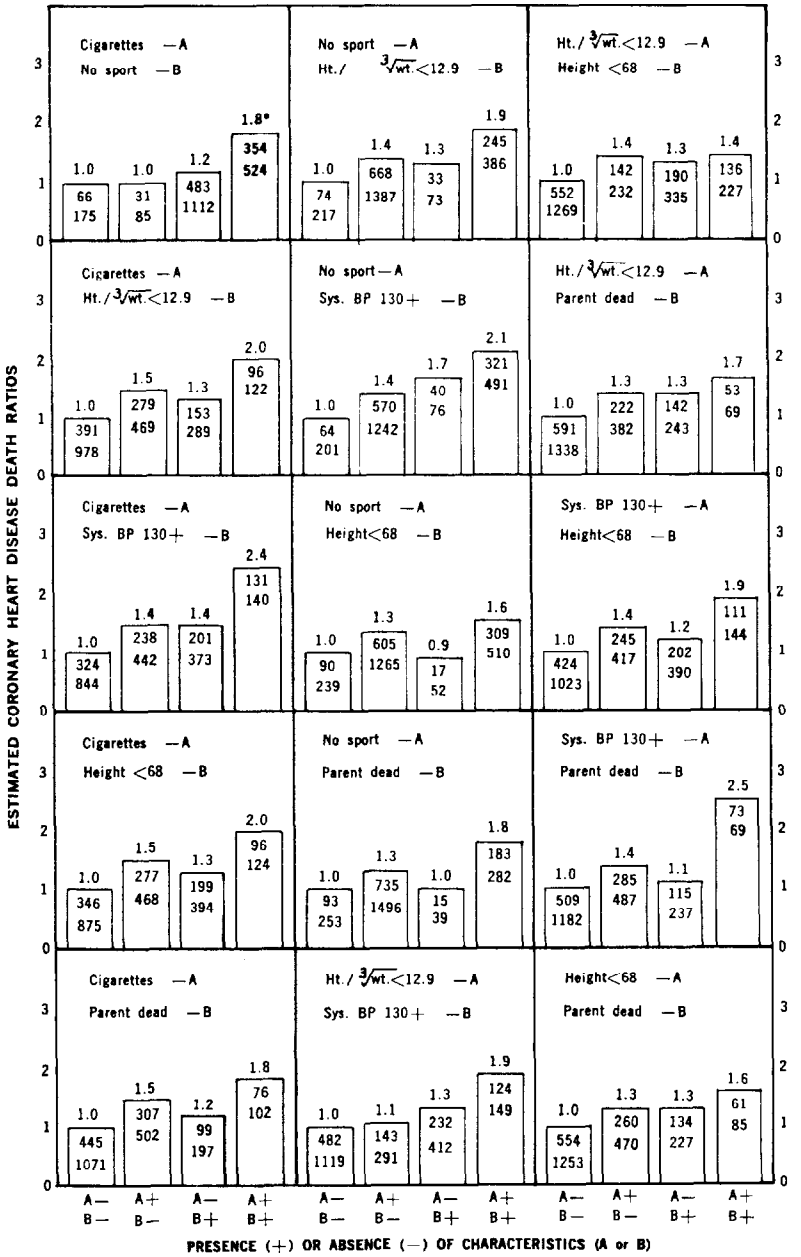


FIGURE 2—Risk of coronary heart disease (12 years) according to cigarette smoking habit and presence of "predisposing factors" (men 30–59 at entry). Framingham Heart Study.

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



Top numbers in bars are CHD decedents with paired combinations of characteristics; bottom numbers, control subjects with combinations.

*$1.8 = \frac{354}{66} \times \frac{175}{524}$

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 All smokers .1.70 <10 .....1.29 10–20 ....1.89 20–40 .....2.20 >40 .....2.41	(709) (3361) (192) (864) (604) (118)	[2](p<0.001)
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 8	93	NS .....1.00 All smokers .2.40 <20 .....2.00 20 .....1.70 >20 .....3.50	(20) (73) (17) (20) (36)	
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 <10 .....1.55 10–20 .....1.58 >20 .....1.78	 (1380) (337) (766) (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 All smokers .1.74 1–9 .....1.39 10–20 .....1.78 21–39 .....1.84 >39 .....2.00	(2997) (4150) (439) (2102) (1292) (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 1–24 .....1.13 >25 .....1.00	(17) (69) (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 SM>20 ....2.20	(27) (25)	(p<0.05)

[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 (713)	
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 (73)	
						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 (386)						
						Preliminary report.

[2] "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		
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	1.73	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. (*183*).	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*).	68,153 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	239	NS <10 20 >20	1.00 1.65 1.70 3.00	(27) (34) (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 5–9 deaths.
	40–49	*50–59*	*60–69*	*70–79*	
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	1.31	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*	*65–69*	NS includes pipes and cigars. SM includes ex-smokers.
NS	1.00	1.00	1.00	1.00	
±10	4.22	2.05	1.41	1.17	
±20	6.14	3.17	1.64	1.26	
±30	8.57	3.33	1.66	1.36	
>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
10 .....1.90 (23)	1.36 (13)	Pooling Project.
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		*Males*	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.
60 and over		*40–59*	
1.00 (7)	SM	....1.80(2)	
1.27(11)		*60 and over*	
1.96(23)	SM	....0.86(6)	
Females—Continued			
1.00(47)			
1.31 (5)			
0.42 (2)			

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.	3	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*			Comments
		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	Total myocardial infarction includes those dead within 48 hours.
2.00	SM 1.82	1.00	1.00	1.00	1.00	1.00	1.00	
(p>0.01)	(p<0.01)	2.47	3.06	1.69	2.25	2.87	1.80	
1.77		0.52	2.15	1.32	1.25	2.31	1.65	
		3.04	3.29	1.81				
5.92		10.09	7.69	5.30	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 40–59 years of age at entry.	Interviews and regular follow-up examination.	5	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 (25) 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*	† Includes NS, EX, and <20 cigarettes/day.
	†Low SM 1.00(25)	1.00(125)	1.00(157)	‡ >20 cigarettes/day.
	‡High SM 2.17(10)	0.90 (31)	1.41 (53)	Includes all CHD but *excludes death*.
				No data available comparing smokers and nonsmokers.
1.00(53) 1.25(54)				
Noncoronary controls (1,786) 33 7 11 12 30 2 6 ($p<0.005$)				88 developed clinical coronary disease, 47 angina pectoris, 28 myocardial infarction, 13 deaths CHD.

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

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. 1,913 males, Albany, 39–55 years of age.	Detailed medical examination and follow-up.	10 8	81	NS .....1.00 (30) 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.
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. (*172*).	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.	3	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 ..1.56 1.67 0.97 <40 .....1.67 1.53 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 A6 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 A7 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 A8). 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		Nonsmokers	
		Person-years of observation	Death rate[1]	Person-years of observation	Death rate[1]
45–54	<130	1,877	27	2,413	8
	130–149	2,066	34	2,912	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	[3]25
	150–169	647	93	1,558	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		Nonsmokers	
		Person-years of observation	Death rate[1]	Person-years of observation	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	20
55–64	<80	1,059	104	1,447	[2]21
	80– 89	1,521	59	2,704	15
	90- 99	669	194	1,521	[3]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		Nonsmokers	
		Person-years of observation	Death rate[2]	Person-years of observation	Death rate[2]
45–54	Hypertensives	883	125	1,871	[3]32
	Nonhypertensives	4,169	29	5,303	13
55–64	Hypertensives	931	150	2,219	95
	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 140/90 mm. Hg.

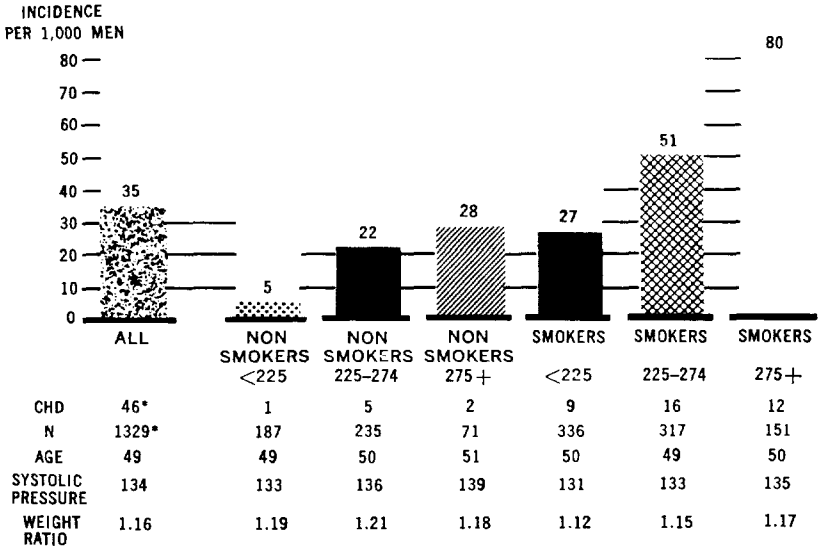
(2) Hypertension—systolic blood pressure 160 mm. Hg. or over, or diastolic 95 mm. Hg. or over, or both.

(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).



	ALL	NON SMOKERS <225	NON SMOKERS 225–274	NON SMOKERS 275+	SMOKERS <225	SMOKERS 225–274	SMOKERS 275+
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.

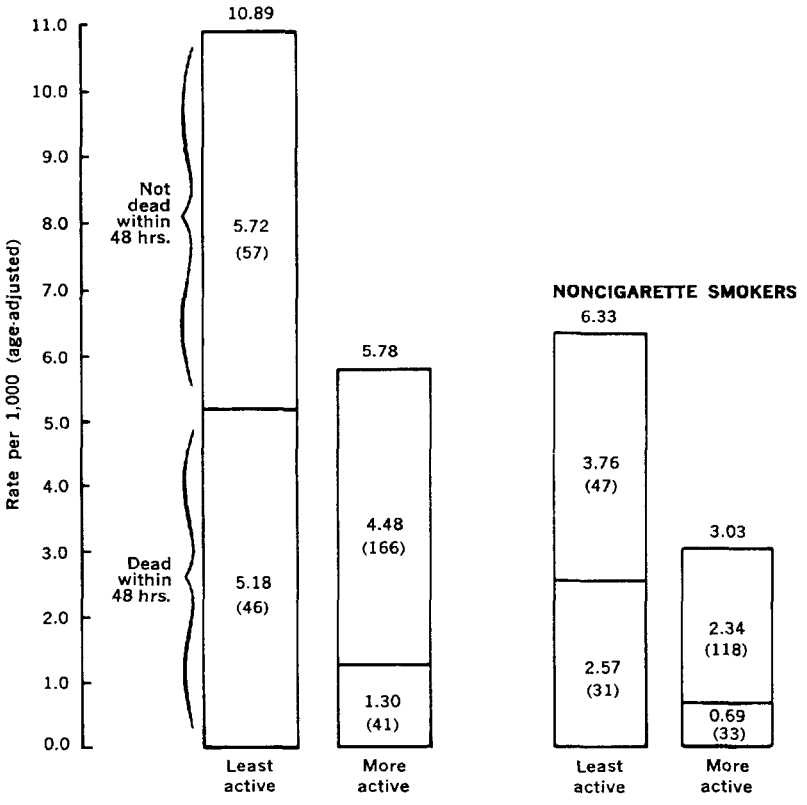
SOURCE: Stamler, J., et al. (*177*).

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	52.0
NH	H	NH	491	57	115.8	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			[2]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 $\geqq 80$; $\geqq 10$ cigarettes per day; diastolic blood pressure $\geqq 90$ 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. (*23*).

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. (*76*).	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. (*172*).	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		20–24	
		Current smokers	Discontinued for five or more years	Current smokers	Discontinued for five or more years
		(Probability $\times 10^5$)			
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	1,213
	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. (*45*).

Based on data derived from Kahn, H. A. (*93*).

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 A17, A18), 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 pair.

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

(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. (*214*).	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. (*12*).	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 (30) / 1.3 (32) / †6.3 / 2.2 40–49 . . †23.6 (34) / 11.5 (27) / †15.8 / 4.4 50–59 . . †36.3 (39) / 14.8 (39) / †27.9 / 9.9 60–69 . . †31.9 (32) / 23.8 (36) / †26.5 / 22.5 70–79 . . 41.9 (18) / 31.7 (36) / 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 450 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. (*182*).	747 males 20–64 years of age autopsied betwen 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 (*34*) 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_2. 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-0_2 for 6 weeks. 9 percent 0_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 0_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.	3½	1,050	NS .....1.00 (164) Cigarettes SM .....†1.30 (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 (*50*).	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 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 underlying to CVD as cause	Cigarettes per day	Pipes and cigars	Age variation	Comments
Kahn, 1966, U.S.A. (*93*).	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 ....1.30(1,394) Current cigarettes ..1.52 (692) 1–9 .....1.51 (98) 10–20 .....1.42 (325) 21–39 .....1.70 (215) >39 .....1.59 (37)	*Pipes* SM ..1.06 (82) NS ..1.00(614) *Cigars* NS ..1.00(614) SM ..1.08(135)		
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* / *Males* / *40–49* / *50–59* / *60–69* / *70–79* 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 1.83 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*).	3,263 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 (615)* 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 A 30, 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., 1968, 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. (*163*).	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 (*135, 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., 1966, 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.

(Actual number of cases shown in parentheses)*

[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) / *Ages40–59* (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) / 229.5(589) <10 ..... 217.4 (75) / 229.1 (76) 10–19 ..... 221.1(134) / 230.1 (95) 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*: NS 214(38); 5 cigarettes/day 201(12); 10 213(34); 20 201(33); >30 206 (8). *Mean Beta/Alpha lipoprotein ratio*: NS 2.0(36); 5 cigarettes/day 2.1(11); 10 1.9(33); 20 1.9(35); >30 1.8 (8).	
Bronte-Stewart, 1961, South Africa (*31*).	Approximately 600 healthy males 25–55 years of age.	*Cholesterol mg. percent*: NS 25–39 †A 179, ‡E 197; 40–55 A 222, E 246. "Heavy" SM 25–39 186, 223; 40–55 204, 236. *Beta/Alpha lipoprotein ratio*: NS 25–39 A 2.89, E 3.34; 40–55 A 3.75, E 4.59. "Heavy" SM 25–39 3.82, 4.40; 40–55 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: NS .. ; <20 cigarettes/day 208(5) ; >20 cigarettes/day 197(5) 40–49: NS 195(12) ; <20 cigarettes/day 201(16) ; >20 cigarettes/day 175 (7) 50–59: NS 189(10) ; <20 cigarettes/day 202(13) ; >20 cigarettes/day 171 (7) 60–69: NS 176 (7) ; <20 cigarettes/day 195(10) ; >20 cigarettes/day .. *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 ; 65.7 ; ..	No statistically significant differences found between SM and NS.
Kedra and Dmowski, 1966, Poland (99).	200 clinically healthy males 20–50 years of age.	*Serum cholesterol mg. percent* NS(100) 170.2 ; SM 100) 224.9 ; p<0.01 *Phospholipids mg. percent* NS(100) 268.1 ; SM 100) 257.5 ; p>0.05 *Total lipids mg. percent* NS(100) 1,234.8 ; SM 100) 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* NS(100) 43.1 ; SM 100) 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-Stucky 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 SM (738) ..... 247 $p<0.01$	
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* NS(20) ..... 176.3 / 68.6 / 193.4 Light SM(17) ..... 172.1 / 68.4 / 188.9 (Over 7.3 cigarettes/day) Heavy SM(27) ..... 200.0 $p<0.05$ / 87.6 $p>0.05$ / 215.0 $p<0.001$ (Over 22.5 cigarettes/day)	Significant figures refer to heavy smokers as compared with nonsmokers.

[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		141.5	
		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		83.9	
		SM (407)	133.6	($p \leqq 0.05$)	82.5	($p \leqq 0.05$)

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 Kielsburg, 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*: *Males* / *Females*; *Age adjusted mean diastolic blood pressure*: *Males* / *Females* NS ..... 137.9 (360) / 84.5 (1439); 136.6 (360) / 82.1 (1439) Cigarette ... 136.4 (1426) / 81.4 (910); 131.6 (1426) / 79.0 (910) ($p<0.001$)	
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)*: *UK* / *U.S.A.*; *Mean diastolic blood pressure*: *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	The author did note SM-NS blood pressure differences prior to controlling for weight, but not after such control.
Tibblin, 1967, Sweden (*187*).	895 males in Göteborg, Sweden, born in 1913.	*Blood pressure* ≦*110*/≦*70* (*89*); *115–145/75–95* (*468*); *150–170/100–110* (*220*); >*175*/>*115* (*75*) NS ..... 18.0; 23.0; 25.5; 34.7 1–14 cigarettes ..... 29.2; 29.2; 25.5; 18.7 >15 cigarettes ..... 28.1; 20.9; 15.5; 17.3 Pipe and cigar 11.2; 8.6; 10.0; 4.0	Numbers in parentheses represent total in blood pressure group. The author noted a stepwise decrease with level of blood pressure as smoking increased.

[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	Never smoked	Smoking group					
		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)	4.9(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	0.396	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	63.527	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. (*208*).	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 15/15 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
Balazs 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^{34} 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 Blesa, 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 0_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 Ahn, 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
Penteost and Shilling-ford, 1964, U.S.A. (129).	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. (62)	5 male and 3 female patients with healed myocardial infarction 48–69 years of age 2/8 nonsmokers.	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.

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. 36–64 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. (*3*).	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. (*208*).	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. (*2*).	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):
		II. (10) Cholesterol plus 0.0015 g. nicotine/day intravenously.	I. 2.5.
		III. (4) Nicotine only.	II. 3.4.
			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. (*127*).	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
Hass 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 stock 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. (*109*).	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. (*206*).	48 male New Zealand white rabbits.	I. Untreated control—12 subjects. II. Regular diet plus 0.1 percent cholesterol—12 subjects. III. Regular diet plus 2.28 mg./kg./day nicotine in water—12 subjects. IV. Diet plus— (a) 0.1 percent cholesterol (b) 2.28 mg./kg./day nicotine in water—12 subjects.				Group II and IV showed an immediate increase in plasma cholesterol and phospholipids with a leveling 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*).	5 mongrel dogs.	Intravenous infusion of 20 mg./kg. nicotine in 20 minutes.	Definite increase in 13/15 observations.				
Kershbaum et al., 1965, U.S.A. (*107*).	20 adult mongrel dogs.	I. 9 received IM nicotine daily for 6 weeks; up to 1 mg./kg. II. 5 placebo injection. III. 6 control.	I. Significant increase in 8/9 dogs. II. No change. III. No change.		No change in any group.		

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

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

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

Author, year, country, reference	Number and type of population	Smoking procedure	Results
Kjeldsen and Damgaard 1968, Denmark (*115*).	8 male students 23–27 years of age.	Five daily one-half hour exposures to 0.5 percent CO for 8–10 days. Overall mean COHb 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 $2\frac{1}{2}$ 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 stypven time* (−)	
Mustard and Murphy, 1963, U.S.A. (141).	7 white males with either CVD or COPD, all heavy smokers 35–72 years of age.	Compared after periods of abstinence or continuation of smoking.	(−)	(−)	(−)		(−)	(−)	(+) decrease	(+) increase	*Platelet clumping time* (±)	
Ambrus and Mink, 1964, U.S.A. (4).	20 healthy 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 $p<0.01$.

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
Sogani and Joshi, 1965, India (*174*).	11 observations on male smokers all regular tobacco users.	Smoked 2 cigarettes or 2 biris or chewed 1 betel nut quid in 20 minutes.	(−)	(−)		(−)	(+) increase				*Fibrinolysis* (+) decrease	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 Korolko, 1965, Poland (*100*).	39 male and 11 female smokers and 24 male and 26 female nonsmokers 18–25 years of age.	5 cigarettes in 1 hour.	(±) decrease	(−)		(+) decrease					*Thrombin time* (±) decrease	
Murchison and Fyfe, 1966, Scotland (*139*).	8 males and 4 female patients with various diseases, all heavy smokers 37–67 years of age.	2 cigarettes in 15 minutes. lit or unlit cigarettes.					(†)	(+) increase				† Smoking both lit and unlit cigarettes caused a rise in platelet adhesiveness which the authors correlated with rise in plasma non-esterified fatty acids.

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

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

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

Author, year, country, reference	
Rottenstein et al., 1960, U.S.A. (*162*).	8 males (18–41 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. (*8*).	30 healthy individuals (19–59 years of age) were studied for the effect of smoking two cigarettes on extremity pulse volumes and skin temperature. Smoking was found to be associated with a 2–6 percent decrease in skin temperature and a 45–50 percent decrease in blood pulse volumes to segments of the finger, calf, and toe.

CHAPTER 3

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 (*80*).	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 ...13.65(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*).	440,558 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) ..6.55(194) SM (age 65–79) .11.41(175)	
Kahn, 1966, U.S.A. (*132*).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	*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 8 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* Vital capacity .....4.50 $FEV_{1.0}$ .....3.38 $FEV_{1.0}/FVC$ .....75.0 PEFR .....6.97 MEFR 50% .....3.81 MEFR 25% .....1.31 Inspiratory resistance .2.07 Expiratory resistance .2.80 Compliance ..... No change	*Value after cessation* 4.57 3.52 76.8 7.45 3.93 1.50 1.43 2.04	*Significance* Not significant. $p<0.05$. Not significant. Not significant. Not significant. $p<0.05$. $p<0.025$. $p<0.02$.	Mean duration of the non-smoking period was 40 days.
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)* NS(22): None 13.6; Few 22.7; ⅓ of surface 31.8; ½ of surface 22.7; Most of surface 9.1; Whole surface .. SM(49): None 12.2; Few 10.2; ⅓ of surface 10.2; ½ of surface 18.4; Most of surface 26.5; Whole surface 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. (*129*).	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* NS(23): Trachea 52.8; Bronchus 47.7 Light(31): Trachea 62.0; Bronchus 57.5 Heavy(10): Trachea 66.2; Bronchus 61.9 *Mean ciliary height in trachea and bronchus on cigarette smokers and nonsmokers* (23): Trachea 6.39; Bronchus 5.95 (29): Trachea 5.62; Bronchus 5.49 (10): Trachea 4.89; Bronchus 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; 24.9; 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* *Category* — *Mean Severity* — *Statistical Significance* SM (114) ..... 2.3 } ($p<0.001$) NS (51) ..... 0.9 Male (107) ..... 2.2 } ($p<0.001$) Female (58) ..... 1.2 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 (*163*).	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	33.5	28.4	4.4	
		20–40 cigarettes/day (254)	5.9	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 / 0.9583 / 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.

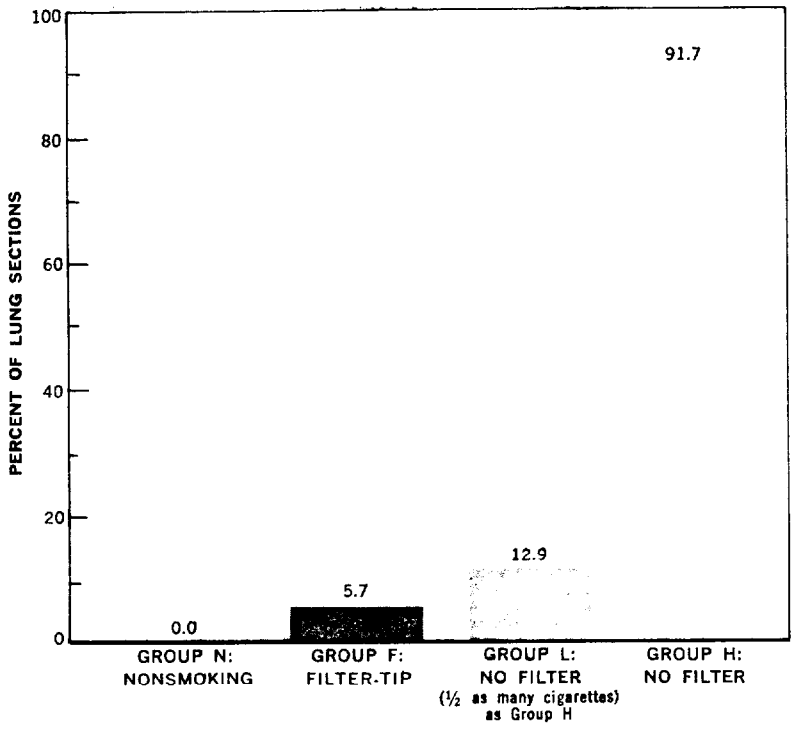

FIGURE 1.—Percent of lung sections with grade IV or V fibrosis.
SOURCES: Hammond, et al. (*104*).

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.

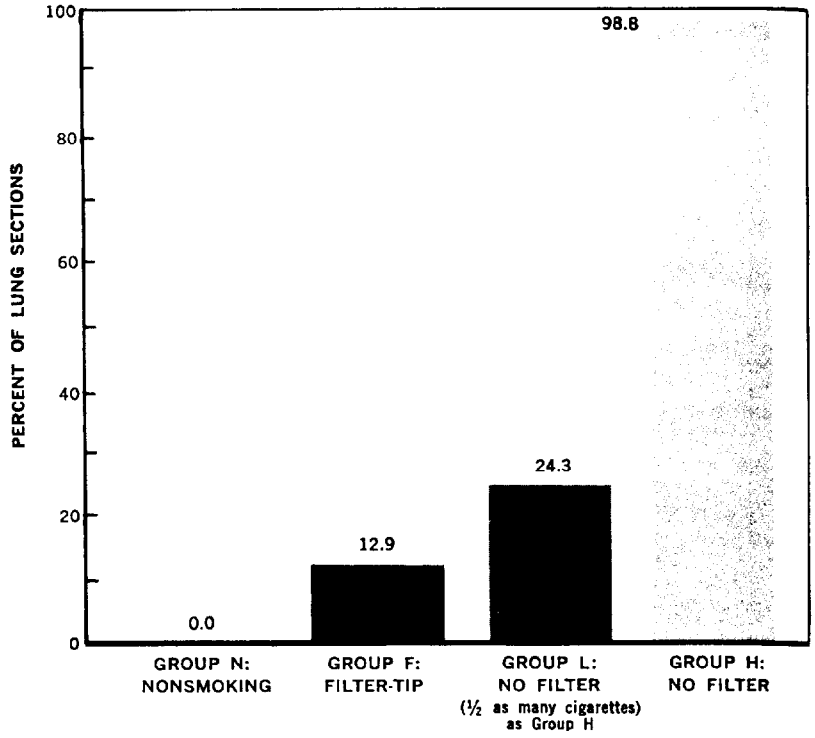

FIGURE 2.—Percent of lung sections with grade II or III emphysema.
SOURCES Hammond, et al. (*104*).

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.
Eich, 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. (*13*).	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 $p0_2$ 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.	
Albert et al., 1969, U.S.A. (*2*).	36 subjects undergoing 117 experiments.	Radioactive tagged $Fe0_2$ particles measured with Scintillation counter.		† 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.

	Number of subjects	*Average age*	*50 percent clearance time (minutes)*	*90 percent clearance time (minutes)* †
Nonsmokers	9	28	88	357
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	375
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. (*3*).	Donkeys exposed to cigarette smoke by nasal catheter.	Radioactive tagged FeO_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.

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., 1959, 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*).	363 male London transport employees 40–50 years of age.	NS .... (30) 1–14 g./day 15.5 (156) >15 .....27.3 (116)	NS ..... 8.7 1–14 g./day ..29.9 >15 .....36.9	NS .... 1–14 g./day .. 8.2 >15 ..... 8.6	NS ..... 4.3 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 (253) SM .....23.3 (1,198) <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 .....45.0 >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 .....75.3 *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 ..... 25.3 (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 ..... 4.5 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., 1965 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* NS ..... 3.8(1,900) 3.2(3,137) SM ..... 6.3(1,098) 6.3 (554) EX ..... 2.9(1,782) 4.3(1,151) <1 cigarette/day .....5.8(876) 1–2 .....6.5(417) 3–4 .....5.6(124) >5 .....9.9(142)		*Males* *Females* 2.4 2.1 6.1 8.3 3.9 4.2 5.8 8.4 8.1 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 (12,351) 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 (*146*).	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(149)	38 (37)				
		>20 ....27(148)	28(136)	42(121)	25 (12)				
			Females						
		NS ..... 3(500)	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 ..... 5.0 (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 particuar smoking group)

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

Author, year, country, reference	Number and type of popuation	Cough		Bronchitis			Comments
			Observed/ expected cases	*Hypermorbidity ratio*	*Observed expected cases*	*Hypermorbidity ratio*	
Cederlof et al., 1966, Sweden (*46*).	9,319 twin pairs registered in Sweden of 12,889 available.	Group A:					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 Groups A and B are between smoking-discordant pairs. 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.
		Males	393/151.9	2.6	157/50.8	3.1	
		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 (653)	
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 avialable).	*Prevalence of respiratory symptoms*					Group A—as above. Group B—as above. 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	
		1-10	6.4	6.4		2.7	
		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, 1959, England (*52*).	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 (56)	101 (29)			
		EX	143 (31)	89 (62)			
		1–14 grams	.140 (193)	87 (157)			
		>15 grams	.133 (89)	80 (136)			
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 ..... [3]4.44 (14)	SM .....[2]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) 3.88 (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 [1]2,489 [2]2,656 [3]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. (*24*).	1,451 male employees in California light industry.		*MMEFR* NS ..... 15.5 (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 45.0 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.					*$D_L CO$* NS ..... 33.10 (30) SM <5 years .[2]28.40 (8) 5–10 years ...[3]28.20 (10) >10 years ...[5]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 [2]31 Exercise: 2 minutes ..50 [3]41 4 minutes ..50 [1]43 3 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* 4.34 [1]5.09	5.77 [1]5.53		Authors found a significant difference between SM and NS for RV/TLC, compliance, and non-elastic 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 [3]0.77 0.74 45–49 [5]2.95(170) 2.64 (42) 3.92 3.83 [3]0.74 0.70 50–54 [1]2.75(115) 2.62 (22) 3.71 3.74 [2]0.74 0.70 55–59 [1]2.64 (64) 2.44 (18) 3.54 3.61 [5]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
			PEFR†		*$FEV_{1.0}$*‡		*Forced VC*‡			
			Males	*Females*	*Males*	*Females*	*Males*	*Females*		
Huhti, 1965, Finland (*126*).	653 male and 823 female residents of a rural region in Finland.	NS	569 (122)	410 (709)	3.46	2.42	4.40	3.18		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.
		EX	551 (141)	403 (30)	3.39	2.32	4.51	3.19		
		Cigarettes/day:								
		1–14	518 (108)	431 (77)	3.17	2.74	4.40	3.53		
		15–24	537 (191)	493 (7)	3.30	2.82	4.51	3.50		
		>25	517 (85)		3.08		4.26			
Krumholz et al., 1965, U.S.A. (*142*).	20 male medical students or graduate physicians.								*Pulmonary compliance* NS 0.241 (10) SM [5]0.177 (10) *Compliance/FRC* NS 0.054 SM [2]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 31.1 SM [3]25.9	NS includes pipe and cigar smokers and ex-smokers of greater than 1 pack year. D_L values have been corrected for COHb.
									D_L/alveolar volume 6.22 [4]4.96	

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. .[5]151(118) EX ..... 157 (93) Pipe, cigar .. 167 (47)	7.89 8.09 8.20	*$FEV_{1.0}$* 2.83 [3]2.64 2.80 2.91	*Vital capacity* 4.93 [3]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 .....[2]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		*$FEV_{1.0}/VC$* [2]87.5 85.3 83.9 83.2	Heavy smoker refers to greater than or equal to 4 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(143) Cigarette SM 3.48(511) 1–14 ..... 3.67 (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* NS ..... 553(106) 527(101) 444(27) Grams/day: 1–14 ..... 557 (26) 519 (17) 410 (7) 15–24 ..... 532 (94) 446 (35) 401(13) >25 ..... †528 (66) †494 (31) †380(10)	$FEV_{1.0}$ *35–44* *45–54* *>55* 3.70 3.22 2.76 3.64 3.31 2.24 3.66 2.94 2.28 3.54 3.05 †2.12		1 cigarette = 1 gram. 1 ounce tobacco = 26 grams. 1 cigar = 2 to 5 grams. † Derived slopes found significantly different from 0.
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* NS ..... 4,470(14) 3,310(40) SM ..... 4,500(13) [1]3,200(20)	*Younger* *Older* 5,125 4,290 [1]5,285 [1]4,290	*Nitrogen gradient* *Younger* *Older* 1.53 2.49 [1]1.47 [5]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* 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 (891) ≥25 grams/day ..... 3.02(1,011) 2.95 (149)			FEV expressed as standardized for specified postal and transit workers at age 45 and at sitting height of 35 inches. Includes mixed smokers.

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 ..... 97.5 (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 Wonnacott, 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 (*159*).	37 MZ and 62 DZ twin pairs selected from Swedish Twin-Pair Registry.	$\frac{FEV_{1.0}}{}$ 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.	$\frac{N_2 \text{ washout gradient}}{}$ 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.*
	Aleveolar 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 (*112*).	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. (*233*).	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. (*128*).	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. (*106*).	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. (*32*).	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 trachael 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^{-5} 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. (*189*).	*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 5–28 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. (*236*).	*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. (*26*).	*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. (*235*).	*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 ciliastasis* 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. (*135*).	*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. (*133*).	*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. (*138*).	*In vivo:* Common mollusk ciliated epithelium.	Cigarette smoke dissolved in sea water.	Significant ciliastasis, reversible.
Battista and Kensler, 1970, U.S.A. (*28*).	*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.
Giammona 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*: *Number*; *20 percent area*; *100 percent area*; *Stability index*. Control: 11; 7.1; 60.7; 1.60. Smoke: 10; 18.7 ($p<0.002$); 45.8 ($p<0.002$); 0.84.

TABLE A15.—*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* Mean age ..... 49.6 / 49.6 NS ..... 15.25 / 25.21 Cigarettes only ..... 63.56 / 52.33 Mixed ..... 21.19 / 22.46	The author stated that there was a significant difference in tobacco usage between the two groups.
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* (*Cases* / *Controls*); *Females* (*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 30–39 ..... 11.3 / 9.3; 11.4 / 2.4 >40 ..... 9.4 / 6.7	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
Dowling, et al., 1957, U.S.A. (*72*).	Individuals exposed to "infectious cold agent" and placebo.	Interview and medical examination.	*Exposed to placebo* (*Number* / *Percent developing "cold"*); *Exposed to infectious agent* (*Number* / *Percent developing "cold"*) NS ..... 111 / 10; 328 / 34 SM ..... 78 / 14; 249 / 35	No statistically significant differences noted.

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. (*53*).	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. Tuberculous employees were found to have significantly fewer nonsmokers and more smokers.
			NS	†10 (19.7)	178 (168.3)		
			SM	36 (26.3)	215 (224.7)		

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 / 19.9 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): 2.54 / 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 (725) / 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. (*83*).	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

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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 ... 2.57 (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 ..16.50; 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 . 3	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 . 2.57 (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. (*139*).	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 (315) >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 ..... 3.48 (39) 21–39 ..... 9.33 (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* 183 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 .. 3.70 (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. (*306*).	68,153 males in various occupations in California.	Questionnaire and followup of death certificate.	5–8	368	NS .... 1.00 ±10 .... 3.72 ±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 (35)	15.81 (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-

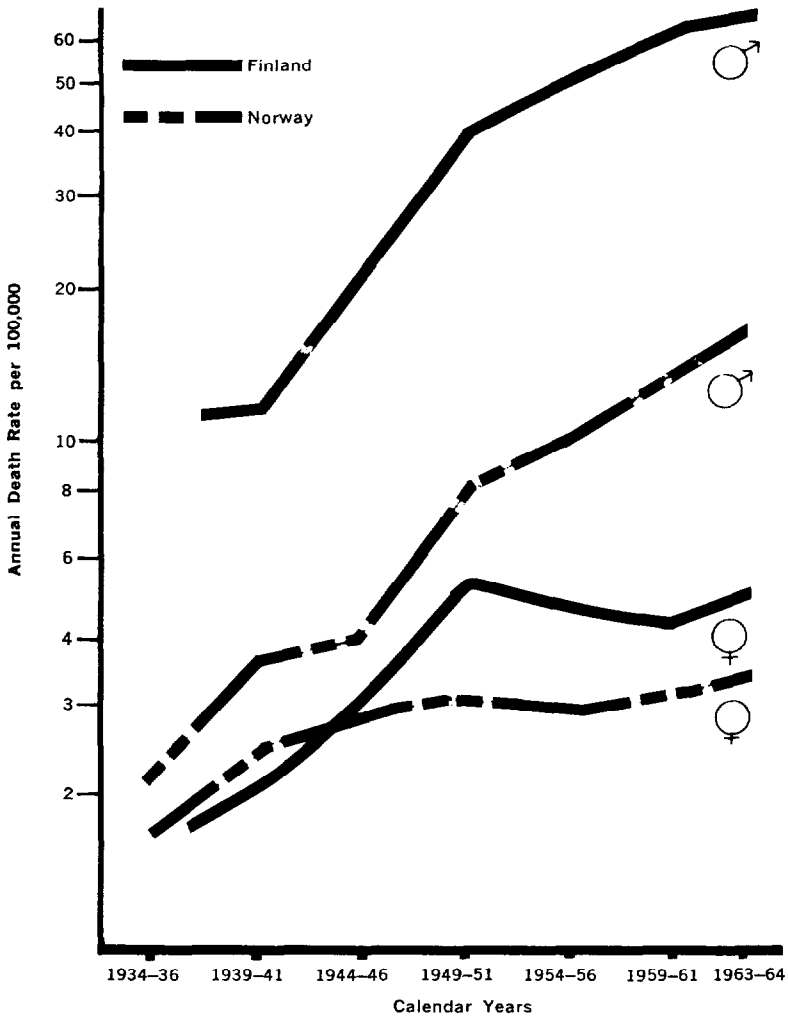

FIGURE 1.—Lung cancer, Finland and Norway.
SOURCE: Kreyberg, L. (154).

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	
1963–65	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. (*316*).	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		
			Oat-cell or		
			Epidermoid (475)	*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		
			Oat-cell or		
			Epidermoid (18)	*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)* Nonsmokers: *Squamous* 1.0 (3); *Undifferentiated* 10.0 (17); *Adenocarcinoma* 23.0 (8); *Alveolar* 20.0 (1) Smokers: *Squamous* 89.0 (183); *Undifferentiated* 90.0 (145); *Adenocarcinoma* 60.0 (20); *Alveolar* ...	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.
Ashley and Davies, 1967, England (*6*).	442 male and female cases of histologically diagnosed lung cancer.	*Percent cases by histologic type and smoking history* Nonsmokers: *Undifferentiated* 2.8 (4); *Squamous* 2.5 (6); *Adenocarcinom* 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)	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.
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* Nonsmokers: *Group I* 21.0 (18); *Group II and large cell carcinomas* 36.0 (9) Smokers: 79.0 (68); 64.0 (16)	The author noted that the small number of cases allows for no definite conclusions.

[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 85 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 / 1.164 / 0.440 / 0.326 / 0.288 / 1.219	Authors noted that estimates are based on very few deaths.
Stocks and Campbell, 1955, England (*265*).	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 / 394	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) / 9.3 (3) / 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. (*112*).	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 (*303*).	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* *Inner Belfast* / *Outer Belfast* / *Belfast Environs* / *Urban Areas* / *Small Towns* / *Rural* Males: 157(241) / 139(157) / 135(45) / 118(185) / 137(26) / 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. (*49*).	304 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* Nonsmokers: Los Angeles Rate 28.1, Ratio 2.5; San Francisco/San Diego Rate 43.9, Ratio 3.9; All other California counties Rate 11.2, Ratio 1.0 Smokers: <1 pack/day: 63.6, 5.7; 77.1, 6.9; 61.02, 5.4 ±1: 126.0, 11.3; 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 (*126*).	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* *Males*: Low / Intermediate / High Nonsmokers: 11.5 / 3.8 / 4.9 Smokers: 1–14 cigarettes/day: 10.6 / 14.2 / 23.5 >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* Nonsmokers ..... 23.5 (34) Smokers ..... 43.7 (71) Heavy smokers ..... †61.3 (31)	Smokers included pipe and cigar smokers. † $p \leq 0.01$ in comparison with nonsmokers.
Hamilton et al., 1957, U.S.A. (*117*).	Selected autopsy material.		No lung cancer patients included.

	Number	*Age range*	*Percent of cases with: Basal cell hyperplasia*	*Squamous metaplasia*	*Transitional metaplasia*
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 ..... 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)	Nonsmokers include those smoking less than or equal to 5 grams per day.

			No. of Persons	*Percent of cases with: No change*	*Basal cell hyperplasia*	*Squamous metaplasia*	*Atypical proliferative metaplasia*	
Knudtson, 1960, U.S.A. (*147*).	100 persons 23–85 years of age autopsied at Seattle Veterans Hospital on whom smoking data was available.	Nonsmokers	(21)	47.6	28.6	14.3	9.5	Age, occupation, and site of residence were found to have no appreciable effect.
		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	29.5	
		>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
			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*	
Auerbach et al., 1961, U.S.A. (*12*).	339 persons 22–88 years of age autopsied at East Orange Veterans Hospital (excludes lung cancer).	Nonsmokers:					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.
		<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	

Author, year, country, reference	Number of cases and method of selection	*Percent sections showing changes in bronchial epithelium (number of sections)* †						Comments
			Normal	*Hyperplasia*	*Squamous metaplasia*	*Atypical metaplasia*	*Carcinoma in situ*	*Carcinoma*	
Cross et al., 1961, U.S.A. (*64*).	140 persons autopsied at Iowa City Veterans Hospital on whom smoking data was available.	Nonsmokers (31)	61(562)	36(137)	8 (33)	†15 (58)	....	....	† The authors noted that the difference between smokers and nonsmokers was statistically significant.
		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		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. (*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	2.5	
		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	13.3	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	294	41.16				
		Smokers:						
		1–10 cigarettes/day	189	47.09				
		11–20	385	51.43				
		21–30	93	61.29				
		>30	39	69.23				
Nasiell, 1968, Sweden (*198*).	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	45.6	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. I-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	25.0	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	896a	3,183	5.3	LA, RD	—	—
	L	899a	3,195	5.4	LA	—	—
Group H (no filter)	H	135	518	2.5	RC	—	—
	H	259	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	858	5,970	5.3	LA	—	—
	H	876a	6,129	4.9	..	LA, LD, RA	—
	H	877a	6,138	5.4	..	LA	LABB
	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*).

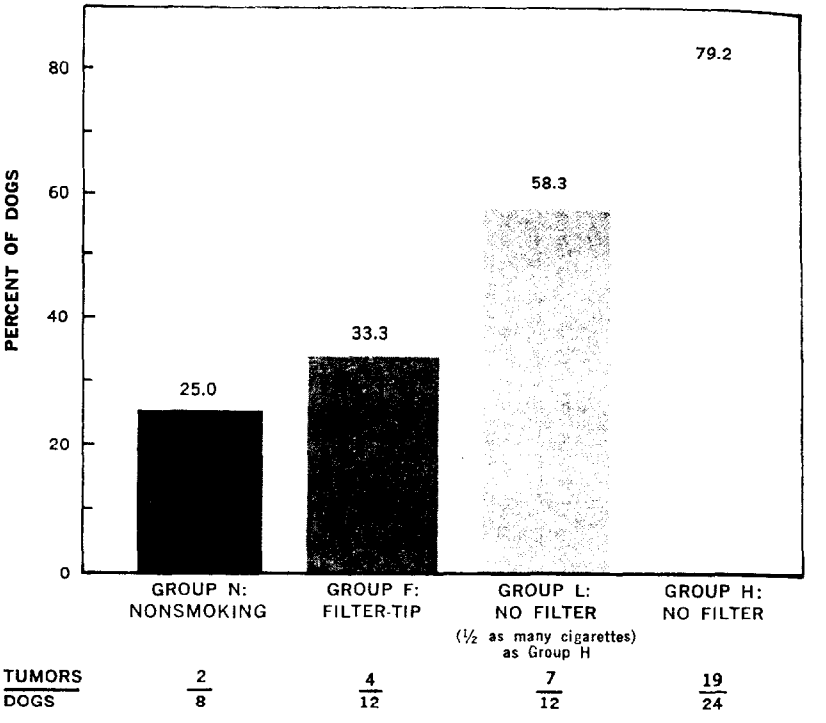

FIGURE 2.—Percent of smoking dogs with tumors.
SOURCE: Adapted from Auerbach, O., et al. (11).

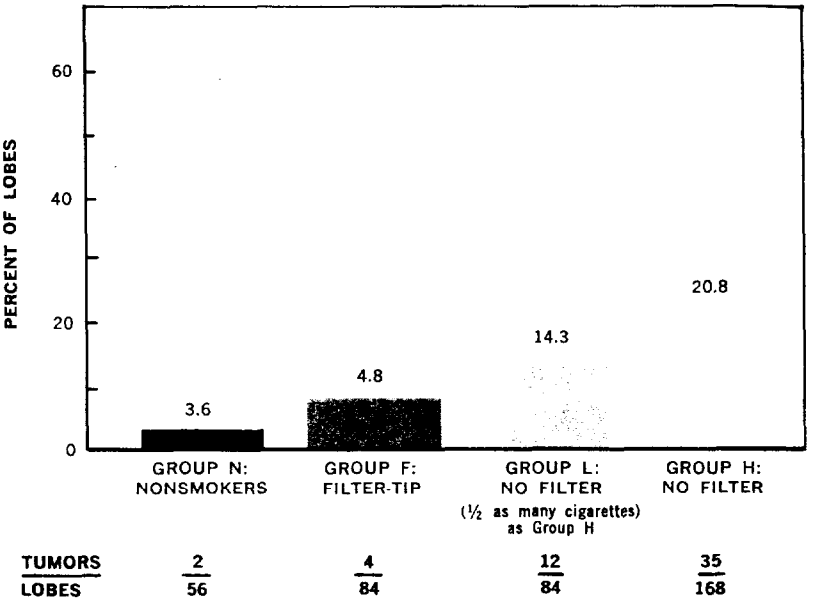

FIGURE 3.—Percent of lung lobes with tumors in smoking dogs.
SOURCE: Adapted from Auerbach, O., et al. (11).

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 3.37 (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 10.5 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*).

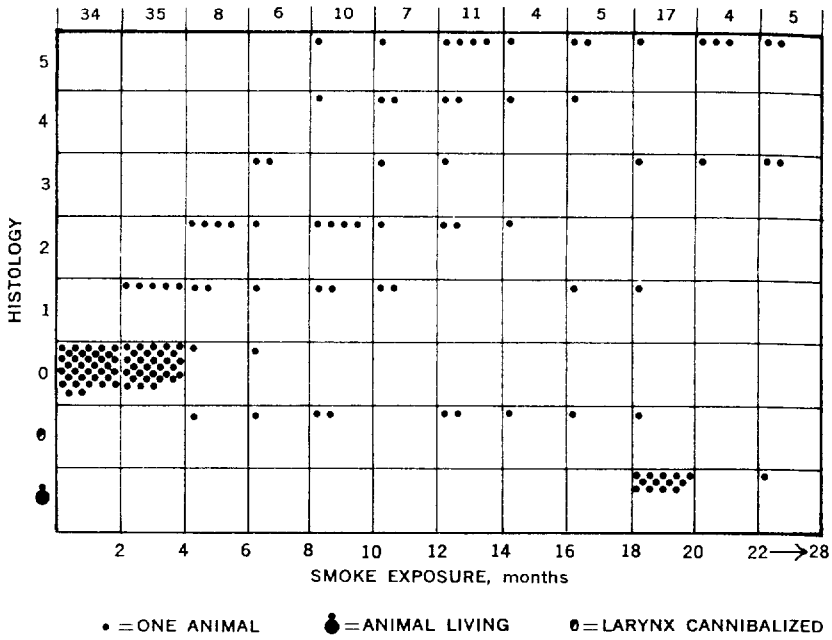

FIGURE 4.—Effects of chronic cigarette smoke inhalation on the hamster larynx. Review of the results of the inhalation experiments: number of smoke-exposed animals with and without changes in the larynx, duration of smoke exposure, and number of animals still alive.
SOURCE: Dontenwill, W. (*76*).

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. (*120*).	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. (*118*).	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) ... 9.90(63) SM (age 65–79) .. 2.93(25)	† Pipe and/or cigar. NS ..... 1.00 (7) SM ..... 4.94(15)	† Male data only. Pipe and cigar data refer to males 55–84 years of age.
Weir and Dunn, 1970, U.S.A. (*306*).	68,153 males in various occupations in California.	Questionnaire and follow-up of death certificate.	5–8	19	NS ..... 1.00 ±10 ..... 3.69 ±20 ..... 1.17 >30 ..... 5.52 All 2.76		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. (*120*).	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* 1.99 (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 (*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 ... 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*).	68,153 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 (16) >39 .....2.75 (5) All 1.45 (46)		1.00 (52) 1.20 (8) 0.94 (10) 1.10 (6) 1.93 (37) 3.20 (34) 2.52 (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.	5–8	*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 ... 1.96 (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 (158) 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 ex-

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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CANCER

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. (*816*).	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 (*73*).	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. 351 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.	1,304 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.	5,636 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, 1958, U.S.A. (*113*).	F	158 lung cancer patients available for interview in 29 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, 1959, 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	749 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 (*308*).	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	32 patients with bronchogenic cancer.	32 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) (*41*).	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							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]		
McConnell et al., 1952 (*180*).	93	5.4	38.5	186	6.5	23.2	1.2	7	57.1	...	14	78.6	...	2.8	
Doll and Hill, 1952 (*73*).	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	29.3	[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*).	265	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 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]		
Randig, 1954 (*218*).	415	1.2	34.2	381	5.8	17.9	[3]5.1	33	51.5	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 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]		
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	26.4	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 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]		
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	2.9	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	58.5	1,811	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. (*123*).		*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.
	NS 8	Site:	
	SM 25	Mainstem bronchus ..... <0.2– 1.7	
		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. (*172*).		*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 tumore 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 ..... 1/50 "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. (*323*).	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. (*28*).	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	36	...	

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:* Standard cigarette Standard cigarette Standard cigarette Standard cigarette Filter cigarette Filter cigarette Acetone only Control	*Surviving at 18 weeks* 24/30 21/30 18/30 13/30 30/30 30/30 66/66 65/65	*Percent Skin cancer* 25.0 5.0 33.0 23.0 7.0 3.0	*Percent Skin neoplasia* 54.0 57.0 44.0 62.0 27.0 23.0	
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: "Tar" and 0.025 mg. B(a)P "Tar" and 0.06 mg. B(a)P "Tar" and 0.25 mg. B(a)P "Tar" and 1.25 mg. B(a)P B(a)P 1.25 mg.	*Survivors* 26 15 15 14 14	*Percent skin tumors* 12.0 27.0 13.0 64.0 ...		Author concluded that cigarette smoke contains cocarcinogens.
Druckrey and Schildbach, 1963, Germany (*82*).	Rats	A. Subcutaneous injection. B. 1/week for 700 days. C. Benzpyrene in tricaprylin.	*Treatment (BP mg./week):* 30 10 3 — (solvent)		*Sarcomas* 25/30 14/40 8/50 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. (*131*).	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	15.0
			Cigarette tobacco	82	27.0	15.0
			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	58.0
			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*
			DMBA ..Ether tobacco leaf extract		4/20	0/20
			O .....Ether tobacco leaf extract		0/20	0/20
			DMBA ..Choloroform tobacco leaf extract		1/20	0/20
			O .....Choloroform 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

† 7,12-dimethylbenz(a)anthracene.

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(10)	..	..

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. (*33*).	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 tracheas. b. Whole bronchial tubes from late fetal dogs and monkeys.	Application of B(a)P in serum.	Squamous metaplasia; 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.
Della Porta et al., 1958, U.S.A. (67).	Syrian golden hamsters.	A. Direct tracheal instilllation. B. Weekly up to 45 weeks. C. 1 percent 7,12-dimethylbenz(a)anthracene (DMBA), cigarette "tar" concentrate.	Material: *Weeks* / *Survivors at 20 weeks/original number exposed* / *Number of hamsters with tracheobronchial carcinomas at death* 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
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., 1966, 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
			Hematite 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. 59.4 (*19*) E. 91.3 (*23*)	No epidermoid cancer noted; papillary adenocarcinoma was most common. Percentage difference is significant at $p < 0.01$ level.
Mühlbock, 1955, Netherlands (*195*).	Hybrid (020 x 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.	*23 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.
Otto, 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* / *Exposure* / *Number with lung tumors* C. 60 None. 3 pulmonary adenomas. E. 189 Varying up to 24 months. 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*: Controls (*11*) 9; Tracheal fenestration (*10*) 10; Nostril inhalation (*9*) 6 *Hyperplasia with atypical features*: 1; 5; 0 *Squamous metaplasia with atypical features*: 1; 6; 0 *Precancerous changes*: 0; 0; 0 *Carcinoma in situ*: 0; †1; 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 acide 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 5,003 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 15		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		*Percent*	
			Male *Female*		*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	
Blümlein, Germany (*26*)	27.5	
Wynder et al., U.S.A. (*312*)	23.6	
Wynder et al., India (*312*)	3.1	
Schwartz et al., France (*248*)	4.6	
Wynder et al., Sweden (*322*)	6.0	
Wynder et al., Cuba (*325*)	(18.9)	(males only)
Dutta-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	10.5
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	Sex	Cases		Controls		Comments
		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. (*193*).	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. (*232*).	M.	1,136	Hospital patients with lip, oral, and pharyngeal cancer, 1938–43: *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 ..... 29 — >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: Number	Cases: Method of selection	Controls: Number	Controls: Method of selection	Comments
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:	
					Percent	
			Males: *Lip* / *Buccal mucosa* / *Anterior tongue* / *Posterior tongue* / *Pharynx* / *Males*			
			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) / (293) / (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) / (152) / (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		*Percent*	
			Male / *Female*		*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 1953–68:	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 (*183*).	M. F.	38	Patients with epidermoid carcinoma of oral cavity and pharynx:	345 114	115 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. (*248*)		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. (*328*)	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. (*298*)	.....	.....	.....	.....	.....	.....	.....	.....	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 (*183*)	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. (*238*).	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 23; Smoke condensate 55; 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 5½ 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 — 40 — 48 — — UV light — 40 — 94 — — B(a)P — 40 — 45 — —

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 cheek 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. (*30*).	ICR Swiss mice.	A. Painting mouse skin.					*Number tumors/ number mice with tumors (small papillomas)*
		B. See results 36 weeks.				*Tobacco equivalent (cigarettes/daily)*	
		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
Protzel et al., 1964, U.S.A. (*213*).	Swiss Webster mice with some having liver damage induced either by CC14 or ethyl alcohol.	A. Swabbing of labial mucosa. B. Up to 13 months. C. B(a)P in acetone.	Alcohol and CCl_4 treated ..... Original number 40; Percent at 13 months with Papillomas 74; Cancer 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: DMBA Alcohol Smoke — Original number 29; Mortality rate 41.0; Number animals 17; Percent with tumors 100.0; Percent with cancer 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; 38.0 ..... Alcohol Smoke — 29; 42.0; 14; —; — .... Smoke — 29; 42.0; 14; —; —

TABLE A31.—*Summary of methods used in retrospectvie 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. (*232*).	M.	104	White patients admitted during 1938–43 to selected hospitals in New York City, Missouri, New Orleans, and Chicago.	615	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.	288 107	Consecutive clinic admissions of patients without cancer. Consecutive admissions of patients with cancers other than intraoral or esophagus.	By means of "detailed questionary." No other details given.
Wynder et al., 1957, Sweden (*322*).	M. F.	39 35	Patients admitted to Radiumhemmet, Stockholm, during 1952–55.	115 156	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.	
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. (*232*).		3.8	13.2	—	—	—	—	4.0	—
Sangvhi et al, 1955, India (*241*).		5.5	17.3	*Average number of bidis smoked*		—	—	3.6	—
				15.3	14.1				
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)*		39.0	38.0	6.6	—
				16.8	16.0				
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., 1968, 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	23.5	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 hospital 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.
Deeley 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	2.3	...	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	85.0	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, Poland (*261*).	M.	6.7	16.0	85.7	65.7	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. (*85*).	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	29.1	1.0	—	1.3	Cigarettes only. More than 15 a day.

CHAPTER 5

Pregnancy

Contents

LIST OF TABLES

INTRODUCTION

In recent years, there has been increased research on environmental factors which may adversely affect the unborn child. The potential effect of maternal smoking on the fetus has been of particular interest because of the large number of pregnant women who smoke and because smoking is an environmental influence which could be controlled. Based on 1970 surveys of smoking habits in representative samples of the U.S. population, it is estimated that one-third of American women in the child-bearing age group of 15 to 44 years are cigarette smokers. What proportion of these give up smoking or cut down substantially on their smoking during pregnancy is not known.

EFFECT ON BIRTHWEIGHT

Epidemiological and experimental studies have supported the view that maternal smoking during pregnancy exerts a retarding influence on fetal growth (tables 2, 6). Analysis of over 100,000 births shows that the infants of mothers who smoke during pregnancy have a mean birthweight of 6.1 ounces less than the infants born to nonsmoking mothers (table 2). Several studies have documented that this effect is independent of other factors known to exert a negative influence on infant birthweight, such as elevated maternal blood pressure and small maternal size (*1, 36, 39*). The reduction in infant birthweight is greater among heavy smoking mothers than light smoking mothers (*12, 21, 23, 30, 41, 50, 58*), and has been found in pregnancies terminating in each trimester (*12, 16, 23, 40, 51, 54*). In a study of more than 48,000 women, Underwood, et al. (*51*) demonstrated that infants born to women who smoked during part of their pregnancy were significantly smaller than infants born to nonsmokers, and that infants born to women who smoked throughout their pregnancy were significantly smaller than the infants born to women who smoked during part of their pregnancy. Russell, et al. (*39*) have presented evidence that although infants born to smoking mothers weighed less than those of nonsmoking mothers, they grew more rapidly during the first six months of life. At one year of age, children born to smoking mothers weighed nearly the same as those born to nonsmoking mothers. They concluded that smoking exerts a retarding influence

on fetal growth and that after delivery this is largely compensated for by a period of more rapid growth.

As documented in more than 15 prospective and retrospective studies, smoking mothers have significantly more infants who are premature, as defined by weight alone (<2,500) grams, than do nonsmoking mothers (table 3). Buncher (*4*) studied the mean duration of pregnancy in smokers and nonsmokers in a survey which included 49,897 live births. He found that women smoking 20 cigarettes a day had a mean length of gestation which was approximately one day shorter than that of nonsmoking women. He calculated that this shortening of gestation is enough to account for only 10 percent of the known reduction in birthweight that is associated with maternal smoking.

EFFECT ON OUTCOME OF PREGNANCY

Some controversy has surrounded the question of whether maternal smoking during pregnancy is associated with an increased risk of spontaneous abortion, stillbirth, and neonatal death. Table 4 summarizes the studies which have dealt with this question. Some of the studies did not demonstrate such an increased risk (*7*, *34*, *50*, *51*), while others did (*12*, *23*, *33*, *58*). Many of these reports (*7*, *23*, *33*, *34*, *41*, *49*, *58*) were based on retrospective studies and included women delivering their infants in hospitals and infants whose names appeared on listings of newborn children (table 1). As Russell, et al. (*39*) have pointed out, such studies may be subject to selective bias since they tend to underrepresent women who have aborted. These retrospective studies also did not systematically control for maternal social class, parity, and maternal age, all of which are related to the outcome of pregnancy and also are related to smoking in some populations. In a prospective study of more than 2,000 pregnant women, Russell, et al. (*39*) have demonstrated a significantly higher percentage of unsuccessful pregnancies (that is, abortion, stillbirth, or neonatal death) among women who smoked during their pregnancy than among those who did not. He interpreted his findings to mean that 20 percent of "... unsuccessful pregnancies in women who smoke regularly would have been successful if the mother had not been a regular smoker" (*38*).

The Second Report of the 1958 British Perinatal Mortality Survey published in 1969 is one of the largest prospective studies to deal with this question (*5*). It included 98 percent of the total births registered during one week in March 1958 throughout England, Scotland, and Wales. In this study, a large amount of obstetric and sociobiologic information was obtained on 17,000 singleton births. This study reported that "the mortality in babies of smokers was significantly higher than in those of nonsmokers." The increase in

TABLE 1.—*Summary of methods used in study of smoking and human pregnancy*

Author, year, country, reference	Retrospective or prospective	Number of persons	Data collection	Case selection	Comments
Simpson, 1957, U.S.A. (*44*).	R.	7,499	Questionnaire was filled out 48 hours after delivery for all patients at San Bernardino County Hospital for 3 years. Same form used for 2 years at St. Bernardines Hospital and Loma Linda Hospital.	Multiple births excluded.	The county hospital population was different, with 50.6 percent of the births being "Mexican".
Lowe, 1959, England (*23*).	R.	2,042	Questionnaire was filled out for every woman delivering at one of six Birmingham hospitals over a 5-month period.	Non-Europeans and women with twin births were excluded.	Social workers performed interviews.
Frazier et al., 1961, U.S.A. (*12*).	P.	2,736	(a) Interview. (b) Prenatal clinic history. (c) Birth and stillbirth certificates.	All Negro women seen at Baltimore Maternity Interviewing Service in 1959 who were scheduled for delivery at Baltimore City Hospital and who received prenatal care in clinic of Baltimore City Health Department.	Nonsmokers include occasional smokers.
Herriot et al., 1962, Scotland (*16*).	R.	2,745	Questionnaire filled out for Aberdeen city residents who were delivered in Aberdeen City Hospital over a 1-year period.		
Savel and Roth, 1962, U.S.A. (*41*).	R.	1,415	1,500 consecutive patients admitted to Newark Beth Israel Hospital were interviewed.	Included were private and ward patients, Negro and white patients, primigravidas, and multiparas; Cesarean sections, elective inductions, and multiple pregnancies were excluded.	Women were considered smokers even if they smoked only 1 cigarette per day.

TABLE 1.—*Summary of methods used in study of smoking and human pregnancy (cont.)*

Author, year, country, reference	Retrospective or prospective	Number of persons	Data collection	Case selection	Comments
Yerushalmy, 1962, U.S.A. (*53*).	P.	982	Form questionnaire.	Pregnancies terminating in abortion were excluded.	
Murdoch, 1963, U.S.A. (*30*).	R.	500	Personal interview by author.	All mothers delivering at Nebraska Methodist Hospital from September 1962 to January 1963.	
O'Lane, 1963, U.S.A. (*33*).	R.	1,031	Standard U.S. Naval Obstetrical Code Sheet was used with supplemental questions. Additional information was obtained from prenatal history.	1,031 Caucasian women who had single pregnancies delivered vaginally over a 6-month period.	"Smokers" defined as those smoking regularly each day.
Zabriskie, 1963, U.S.A. (*58*).	R.	2,000	History was obtained during the postpartum period from 2,000 consecutive births over a 6-month period.	Twin deliveries were omitted.	
Yerushalmy, 1964, U.S.A. (*54*).	P.	6,800	Personal interview.	All women were members of Kaiser Foundation Health Plan. Only pregnancies terminating in single, live births included. All races except whites and Negroes were excluded.	5,381 whites 1,419 Negroes.
MacMahon et al., 1965, U.S.A. (*24*).	R.	12,192	Mail questionnaire.	Mothers of single, white, legitimate live births. Mothers were residents of Massachusetts and delivered in May or June of 1963.	Birthweight based on birth certificate.

TABLE 1.—*Summary of methods used in study of smoking and human pregnancy (cont.)*

Author, year, country, reference	Retrospective or prospective	Number of persons	Data collection	Case selection	Comments
McDonald and Lanford, 1965, U.S.A. (*26*).	P.	177	Interview.	White, unmarried primigravidas receiving obstetric care over a 2-year period.	
Peterson et al., 1965, U.S.A. (*34*).	R.	7,740	Cooperative study involving 17 hospitals in 13 states, using U.S. Air Force obstetrical code.	Includes only those multiparas whose prior infants weighed >2,500 grams (Caucasians). All pregnancies with any complication were excluded. Cesarean sections and induced delivery were excluded.	
Robinson, 1965, Burma (*37*).	P.	1,614	Interview.	Regular attendees at prenatal clinic.	46.8 percent of women smoked cheroots.
Underwood et al., 1965, U.S.A. (*50*).	R.	4,440	Interview by obstetrical resident. Data was obtained on 16,158 pregnancies from the 4,440 women.	Puerperal women from Roper Hospital and Medical College Hospital. Only infants weighing >1,000 grams were included.	Women from Roper Hospital were of above average economic status. Women from Medical College Hospital included Negro and white patients.
Downing and Chapman, 1966, U.S.A. (*7*).	R.	5,659	Review of clinic records from 1952 to 1958.	Six-year total of obstetrical patients at clinic.	

TABLE 1.—*Summary of methods used in study of smoking and human pregnancy (cont.)*

Author, year, country, reference	Retrospective or prospective	Number of persons	Data collection	Case selection	Comments
Ravenholt et al., 1966, U.S.A. (*35*).	R.	2,023	Epidemiologic questionnaire. Much data collected over telephone. Additional data obtained from birth certificates.	Study population was identified by the listing of newborn infants in a Seattle newspaper during May, June, and July of 1964. Twins were excluded.	95.4 percent of mothers were white.
Reinke and Henderson 1966, U.S.A. (*36*).	R.	3,156	Registration data of prenatal clinic.	Negro women who delivered single, live infants from 1962–64.	
Kizer, 1967, Venezuela (*19*).		2,095	Interview.	Patients receiving care at "concepcion palacias" in Caracas.	
Underwood et al., 1967, U.S.A. (*51*).	P.	48,505	Code sheets submitted from 44 worldwide naval installations. Code sheets were completed by the attending physician upon the mother's admission to the labor room.	Women with single pregnancies delivered of infants weighing more than 500 grams between July 1, 1963, and June 30, 1965.	
Duffus and MacGillivray, 1968, Scotland, (*8*).	R.	2,543	Antenatalclinic records.	All "booked" married city primigravidae attending the antenatal clinics during 1960, 1964, and 1965.	The number of cigarettes smoked was not considered.
Mulcahy and Knaggs, 1968, Ireland (*28*).	R.	3,681	Hospital record review.	Mothers admitted to the Coombe Hospital from April 1963 to October 1964.	

TABLE 1.—*Summary of methods used in study of smoking and human pregnancy (cont.)*

Author, year, country, reference	Retrospective or prospective	Number of persons	Data collection	Case selection	Comments
Russell et al., 1968, England (*39*).	P.	2,110	Data collected by Senior research midwives over a 4- to 5-year period.	Women attending the two main maternity units in Sheffield, who "comprised a reasonably representative sample." Multiple pregnancies were omitted.	Included some threatened abortions and some with "bad" obstetrical histories.
Tokuhata, 1968, U.S.A. (*49*).	R.	2,016	Personal interview or mail questionnaire of surviving family members.	Women selected from Memphis and Shelby County death registry who died of cancer of genitalia or breast since 1950 and who had been married.	Control group taken from same registry. They died of causes other than cancer and were matched for race, age at death, and year of death.
Buncher, 1969, U.S.A. (*4*).	R.	49,897	Data obtained from U.S. Navy obstetrical study from 1963 to 1965. Smoking data obtained by physician at the time of mother's admission to labor room.	Women with single pregnancies delivered of infants weighing more than 500 grams between July 1, 1963, and June 30, 1965.	Includes cases reported by Underwood et al. (*47*) in 1967.
Butler and Alberman, 1969, Great Britain (*5*).	P.	17,000	The British Perinatal Mortality Survey of 1958 when a large amount of obstetric and sociobiologic information was obtained from birth attendants, records, and at interview with the mothers.	98 percent of the total births registered during 1 week in March 1958 throughout England, Scotland, and Wales.	Another 7,000 perinatal deaths were surveyed by identical methods over a 3-month period.
Terris and Gold, 1969, U.S.A. (*47*).	R.	197	Public Health Nurse interviewed each mother on first or second postpartum day.	Premature Negro ward births (<2,500 grams) with no known cause of prematurity. Controls were matched by sex, birth order of infant, age, and marital status of the mother.	

TABLE 1.—*Summary of methods used in study of smoking and human pregnancy (cont.)*

Author, year, country, reference	Retrospective or prospective	Number of persons	Data collection	Case selection	Comments
Mulcahy et al., 1970, Ireland (*29*).	P.	100	Interview by physician.	100 mothers of term infants who were free from all significant medical and obstetrical complications. All were between 20 and 30 years of age and were Para III or less. All had normal deliveries. Half were smokers of 10 or more cigarettes per day.	

TABLE 2.—*Maternal smoking and infant weight*

(Numbers in parentheses indicate absolute number of infants in respective groups)

Author, reference	Infant weight: Nonsmoker	Infant weight: Smoker	Difference in mean weight of infant of smoker versus nonsmoker	Comments
Lowe (*23*)		*<10 cigarettes per day* / *>10 cigarettes per day*		Effect on infant weight was independent of maternal age, parity, or complications of pregnancy.
	Male ..... 7.43 lbs. (607)	7.18 (187) / 7.05 (165)		
	Female ..... 7.23 lbs. (539)	6.74 (163) / 6.67 (147)		
	Total ..... 7.33 lbs. (1,146)	6.98 (350) / 6.87 (312)	170 g. (6 oz.)	
Frazier et al., (*12*).	3,080 g. (1,717)	2,924 g. (1,019)	156 g. (5.5 oz.)	Nonsmokers include occasional smokers.
Herriot et al., (*16*).	No data ..... (1,473)	No data (1,272)	160 g. (5.6 oz.)	Effect on infant weight was independent of maternal age, parity, height, or social class.
Savel and Roth (*41*).	White ..... 3,374 g. (383)	3,141 g. (428)	233 g. (8.2 oz.)	*Cigarettes per day* — *Infant weight* White smokers: 1–10 ..... 3,210 g. (161) 11–20 ..... 3,198 g. (184) >20 ..... 3,010 g. (83)
	Negro ..... 3,173 g. (364)	3,031 g. (240)	142 g. (5.0 oz.)	Negro smokers: 1–10 ..... 3,042 g. (169) 11–20 ..... 3,012 g. (57) >20 ..... 2,968 g. (14)
Murdoch (*30*).	7 lbs. 7.5 oz. (242)	6 lbs. 15 oz. (258)	8.5 oz.	*Cigarettes per day* — *Infant weight* 1–10 ..... 7 lbs. 2 oz. 11–20 ..... 6 lbs. 11 oz. >20 ..... 6 lbs. 10 oz. >40 ..... 6 lbs. 8 oz.
O'Lane (*33*).	2,978 g. (566)	2,938 g. (465)	40 g. (1.4 oz.)	

TABLE 2.—*Maternal smoking and infant weight (cont.)*

(Numbers in parentheses indicate absolute number of infants in respective groups)

Author, reference	Infant weight: Nonsmoker	Infant weight: Smoker	Difference in mean weight of infant of smoker versus nonsmoker	Comments
Zabriskie (*58*).	3,320 g. (1,043)	3,091 g. (957)	229 g. (8.1 oz.)	*Cigarettes per day* — *Infant weight* <10 ..... 3,205 g. (260) 10–20 ..... 3,090 g. (395) 20–30 ..... 2,970 g. (264) >30 ..... 3,190 g. (38)
MacMahon et al., (*24*).	Male ..... 124.0 oz. (3,053) Female ..... 119.9 oz. (2,906)	116.3 oz. (3,173) 111.9 oz. (3,011)	7.7 oz. 8.0 oz.	Cigarettes per day — *Infant weight (ounces)*: Male / Female <10 . 121.2 (653) 116.6 (595) 10–20 . 115.2 (1,262) 112.2 (1,259) 20–40 . 114.6 (1,165) 108.9 (1,088) >40 . 113.2 (66) 111.7 (49)
McDonald and Lanford (*26*).	111.68 oz. (87)	*Light smoker* 110.83 oz. (42) *Heavy smoker* 109.38 oz. (48)	No significant difference between mean birthweights.	
Underwood et al., (*50*).	Group: I ..... 3,522 g. (2,406) II ..... 3,304 g. (557) III ..... 3,126 g. (7,775)	*Cigarettes per day* <10 ..... 3,349 g. 10–20 ..... 3,236 g. †(1,720) >20 ..... 3,169 g. <10 ..... 3,171 g. 10–20 ..... 3,146 g. †(660) >20 ..... 3,092 g. <10 ..... 2,938 g. 10–20 ..... 2,965 g. †(3,040) >20 ..... 3,011 g.	*For >20 cigarettes per day* 353 g. (12.5 oz.) (p<0.001) 212 g. (7.5 oz.) (p<0.001) 115 g. (4.1 oz.) (p<0.001)	Patients were divided into 3 groups: I....Private patients of above average economic status. II....White patients of average economic status. III....Negro patients of low economic status. † Total for all smokers in each group.
Ravenholt et al., (*35*).	Male ..... 7.80 lbs. (171) Female ..... 7.50 lbs. (150)	7.21 lbs. †(167) 7.05 lbs. †(171)	.59 lbs. (9.4 oz.) .45 lbs. (7.2 oz.)	† Smoked >4,000 cigarettes during pregnancy.

TABLE 2.—*Maternal smoking and infant weight (cont.)*

(Numbers in parentheses indicate absolute number of infants in respective groups)

Author, reference	Infant weight		Difference in mean weight of infant of smoker versus nonsmoker	Comments
	Nonsmoker	Smoker		
Reinke and Henderson (*36*).	3,135 g. (1,542)	2,987 g. (1,614)	148 g. (5.2 oz.) ($p<0.001$)	
Kizer (*19*).	Data not available	Data not available	97 g. (3.4 oz.)	Total number of patients—2,095.
Underwood et al., (*51*).	3,395 g. (24,865)	*Cigarettes per day* 1–10 ..... 3,286 g. (7,609) 11–30 ..... 3,196 g. (14,450) >30 ..... 3,182 g. (1,570)	109 g. (3.8 oz.) 199 g. (7.0 oz.) 213 g. (7.5 oz.)	
Mulcahy and Knaggs (*28*).	113.3 oz.	*Cigarettes per day* 1– 4 ..... 111.4 oz. 5– 9 ..... 102.3 oz. 10–14 ..... 102.0 oz. 15–19 ..... 102.9 oz. >20 ..... 102.4 oz.	 1.9 oz. 11.0 oz. 11.3 oz. 10.4 oz. 10.9 oz.	
Russell et al., (*39*).	BP <140/ 90 117.2 ± .7 oz. (984) 140/ 90 114.2 ± 1.2 oz. (340) >150/100 99.3 ± 2.6 oz. (138)	107.2 ± 1.0 oz. (496) 108.9 ± 2.4 oz. (117) 90.8 ± 5.8 oz. (35)	10.0 oz. 5.3 oz. 8.5 oz.	The effect of maternal smoking on fetal weight was independent of maternal parity, age, height, educational level, attitude to pregnancy or work during pregnancy, father's social class, consort's social class, and sex of the child or premature delivery.
Butler and Alberman (*5*).	3,375 g. (11,145)	3,205 g. (4,660)	170 g. (6 oz.)	Reduction of mean birthweight of babies born to smokers was independent of unduly high proportion of babies born preterm, and maternal factors including social class and maternal height.
Mulcahy et al., (*29*).	3.83 kg. (50)	3.43 kg. (50)	396 g. (14 oz.)	

TABLE 3.—*Maternal smoking and prematurity (cont.)*

(Figures in parentheses are the absolute number of premature births)

Author, reference	Premature by		Percent of premature infants				Mean duration of pregnancy		Comments
	Weight	Duration of gestation		Nonsmokers		Smokers			
Simpson (44).	<2,500 g.		*Name of hospital:*						*Number and percent of premature infants:*
			County	7.77	(144)	11.48	(96)		Nonsmokers 6.39 (328)
			Loma Linda	6.16	(86)	12.13	(49)		Cigarettes per day:
			St. Bernardines	5.21	(98)	10.50	(119)		1–5 ..... 7.06 (47)
									6–10 .....11.18 (89)
									11–15 .....11.36 (31)
									16–20 .....13.6 (77)
									21–30 .....25.0 (11)
									>30 .....33.3 (9)
Lowe (23).		<260 days		6.4	(57)	10.6	(58)	279.9 days	278.5 days	At each week of gestation, the mean birthweight was lower in babies of smokers.
Frazier et al., (12).	<2,500 g.			11.2	(175)	18.6	(179)	38.7 weeks	38.4 weeks	Infants of smokers weighed less than infants of nonsmokers for a wide range of pregnancy duration.
Herriot et al., (16).	No data	No data	Social class:							2,745 patients in the study. At each week of gestation, the mean birthweight was lower in babies of smokers.
			I and II	4.0		4.8				
			III	3.5		6.8				
			IV and V	6.3		12.6				
Savel and Roth (41).		36 weeks	White	2.6	(10)	4.9	(21)	White .39.8	39.4	
			Negro	13.7	(50)	11.3	(27)	Negro .38.8	38.8	
	†<2,500 g.		White	1.8	(7)	3.7	(16)			† Premature by weight but mature by date (>37 weeks).
			Negro	3.6	(13)	8.3	(20)			

TABLE 3.—*Maternal smoking and prematurity*

(Figures in parentheses are the absolute number of premature births)

Author, reference	Premature by: Weight	Premature by: Duration of gestation		Percent of premature infants: Nonsmokers		Percent of premature infants: Smokers		Mean duration of pregnancy: Nonsmokers	Mean duration of pregnancy: Smokers	Comments
Yerushalmy (*54*).	<5½ lbs.			5.9	(36)	8.1	(30)			
Murdoch (*30*).	<2,500 g.			3.3	(8)	13.6	(35)			
O'Lane (*33*).	<2,500 g.			5.1	(29)	11.8	(55)			
Zabriskie (*58*).	<2,500 g.			3.83	(40)	9.93	(95)			Cigarettes per day: *Prematurity* <10 ..... 6.54 (260) 10–20 ..... 9.11 (395) 20–30 .....14.39 (264) >30 .....10.53 (38)
Yerushalmy (*54*).	<5 lbs. 8 oz.		White	3.5	(112)	6.4	(138) ($p<0.01$)			Infants of smoking mothers weighed less than infants of nonsmoking mothers in each gestational age.
			Negro	4.9	(46)	13.4	(64)			
		<37 weeks	White	†5.9	(188)	6.5	(140)			† Difference between smokers and nonsmokers not significant.
			Negro	13.4	(125)	16.7	(80)			
McDonald and Lanford (*26*).	<2,500 g.			*Cigarettes per day*						
				4.6	(4)	<10	4.8	(2)		
						>10	8.3	(4)		
Peterson et al., (*34*).	<2,500 g.			*Cigarettes per day*						Overall incidence of prematurity in smokers vs. nonsmokers significant at $p<0.001$.
				2.5	(111)	1–10	3.0	(35)		
						11–20	4.8	(80)		
						>20	3.4	(16)		

TABLE 3.—*Maternal smoking and prematurity (cont.)*

(Figures in parentheses are the absolute number of premature births)

Author, reference	Premature by		Percent of premature infants				Mean duration of pregnancy		Comments
	Weight	Duration of gestation		Nonsmokers	Smokers		Nonsmokers	Smokers	
Peterson et al., (contd.) (34).		<37 weeks		*Cigarettes per day*					
				1.3 (58)	1–10	1.4 (16)			
					11–20	2.3 (38)			
					>20	2.4 (11)			
Robinson (37).	<2,500 g.			16.5 (152)		31.0 (181)			
Underwood et al., (50).	<2,500 g.		Group:		*Cigarettes per day*				Percentages and absolute number of premature births are based on 16,158 pregnancies recorded in 4,440 women. Group I. Smokers vs. nonsmokers $p<0.025$. Group II., III. Smokers vs. nonsmokers $p<0.001$.
			I		4.5 (108)	<10 4.2			
						10–20 5.9			
						<20 7.2			
			II		7.5 (42)	<10 12.6			
						10–20 12.3			
						>20 15.9			
			III		9.9 (770)	<10 14.1			
						10–20 14.8			
						>20 10.2			
Downing and Chapman (7).	No data	No data		2.2 (66)		3.3 (88)			
Reinke and Henderson (36).	<2,500 g.			10.6 (163)		16.7 (270)	37.7 weeks	37.67 weeks	$p<0.001$
		<35 weeks		20.3 (313)		22.8 (368)			$p>0.05$

TABLE 3.—*Maternal smoking and prematurity (cont.)*

(Figures in parentheses are the absolute number of premature births)

Author, reference	Premature by		Percent of premature infants			Mean duration of pregnancy		Comments
	Weight	Duration of gestation	Nonsmokers	Smokers		Nonsmokers	Smokers	
Underwood et al., (51).	<2,500 g.		*Cigarettes per day*					Prematurity by birth weight rose directly to a significant degree ($p<0.01$) with each smoking category.
			5.7 (1,417)	1–10	7.5 (571)			
				11–30	9.4 (1,358)			
				>30	11.2 (176)			
		<36 weeks	5.8 (1,442)	1–10	6.9 (525)			Data suggested that smoking in any trimester decreased birth weight.
				11–30	7.5 (1,084)			
				>30	7.5 (118)			
Buncher (4).						*Births*		† Smokes 20 cigarettes per day.
						Male 39.55 weeks	† 39.35 weeks	
						Female 39.69 weeks	† 39.51 weeks	
Butler and Alberman (5).	<2,500 g.		5.4 (602)		9.3 (433)			
Terris and Gold (47).								A significant ($p<0.01$) difference was found between percent of mothers who smoked and those who had premature deliveries and the control group.

mortality rate was found for both stillbirths and neonatal deaths, and was somewhat greater for stillbirths but not significantly so (see Butler, table 4). The authors state that "... the differences between mortality rates in babies of smokers and nonsmokers practically disappear when they are compared within groups of similar birthweights ... It therefore seems reasonable to conclude that the increased mortality found in babies of mothers who smoke is accounted for by the overall excess of low birthweight babies in this group ..." with their attendant high risks.

In 1964, Yerushalmy (*54*) reported on a group of 6,800 women whose pregnancies terminated in single, live births, excluding stillbirths and abortions. The study was prospective and was controlled for maternal age and parity. He noted that neonatal mortality in infants born to smoking mothers and weighing less than 2,500 grams was significantly less than that of small infants born to nonsmoking mothers. He referred to these small infants of smoking mothers as being "apparently healthier" than those infants weighing less than 2,500 grams who were born to nonsmoking mothers.

As this report showed, when compared to infants weighing more than 2,500 grams, a small (<2,500 grams) infant faces a greatly increased risk of neonatal mortality, whether it is born to a smoking mother or to a nonsmoking mother (*54*). The neonatal death rate for the small infants of smoking mothers was less than that for small infants of nonsmoking mothers, but neither group can be considered "healthy," having sharply elevated death rates. The overall neonatal mortality for babies born to white smoking mothers was 12 percent higher than that for babies born to nonsmoking mothers. This is not significantly greater than the neonatal mortality of infants born to nonsmoking mothers. On the other hand it is also not significantly different from the 31 percent excess mortality reported by Butler, et al. (*5*), which is statistically significant.

Interpretation of the neonatal mortality among the infants weighing less than 2,500 grams in the Yerushalmy study is difficult. By considering only live births, the series may have included a higher proportion of infants whose smaller birthweight was primarily due to a modest growth retarding influence of maternal smoking and not to other more serious congenital defects and intrauterine influences. Butler, et al. (*5*) have shown that smoking mothers have significantly more stillbirths than nonsmoking mothers, and Russell, et al. (*39*) have found this to be true for both stillbirths and abortions.

For reasons which aren't clear, smoking mothers have been found to have a reduced incidence of preeclamptic toxemia as compared to nonsmoking mothers (*51*). However, given the presence of

TABLE 4.—*Comparison of abortion, stillbirth, and neonatal death in smoking and nonsmoking mothers*

NS = Nonsmokers SM = Smokers

Author, reference	Numbers								Rates/1,000 total births						Comments
	Total births		Abortions		Stillbirths		Neonatal deaths		Abortions		Stillbirths		Neonatal deaths		
	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	
Lowe (*28*).	1,155	668			†47						†23.0	†30.0			† Includes first-day deaths.
Frazier et al., (*12*).	1,717	1,019			†11	†16	40	28			†6.4	†15.5	23.3	27.5	† "Fetal death".
Savel and Roth (*41*).	White														
	383	428			2	3	4	2			5.2	7.0	10.4	4.7	
	Negro														
	364	240			8	4	5	3			22.0	16.7	13.7	12.5	
O'Lane (*33*).	1,027	887	91	112					88.6	126.3					
Zabriskie (*58*).	2,850	2,769	250	348					87.7	125.7					
Yerushalmy (*54*).	White														
	3,218	2,163					40	30					12.4	13.9	
	Negro														
	939	480					22	11					23.4	22.9	
Peterson et al., (*34*).	4,455	3,285									0.6	1.2	4.0	0.9	

TABLE 4.—*Comparison of abortion, stillbirth, and neonatal death in smoking and nonsmoking mothers (cont.)*

NS = Nonsmokers SM = Smokers

Author, reference	Numbers								Rates/1,000 total births						Comments
	Total births		Abortions		Stillbirths		Neonatal deaths		Abortions		Stillbirths		Neonatal deaths		
	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	
Downing and Chapman (7).	3,029	2,630	126	107	†32	†29			41.6	40.7	†10.6	†11.0			† Stillbirth plus neonatal death.
Underwood et al., (51).	24,896	28,629									8.4	8.7	†11.3	†12.1	† Excludes perinatal deaths in premature infants ($p>0.05$).
Russell et al., (39).	‡BP:														† Includes abortion, stillbirth, and neonatal death.
	<140/90	984 496			†27	†32					†27	†65			‡ Blood pressure.
	=140/90	340 117			†14	†8					41	68			
	>140/90	138 35			†20	†11					145	314			
Tokutata (49).	White														Data based on use of cigarettes only.
	2,555	743			†246	†112					†96	†151			† Includes stillbirths and miscarriages.
	Nonwhite														
	1,235	350			†174	†64					†141	†183			
Butler and Alberman (5).	11,145	4,660			215	129	146	80			19.3	27.6	13.1	17.2	

Source: Modified and expanded from Butler and Alberman (5).

preeclampsia, smoking appears to increase the risk to the fetus because of low birthweight and increased perinatal mortality (*8*).

In a case-control study of sudden, unexpected death in infancy, Steele, et al. (*46*) observed that the percentage of smokers among mothers of cases of sudden, unexpected death, 61.2 percent, was significantly greater than the percentage among mothers of controls, 39.5 percent.

The possible teratogenic effect of maternal smoking has not been adequately evaluated. Although it does not appear to be a major factor, there have been too few studies to determine whether maternal smoking is a significant teratogenic risk (*5, 23, 28, 50*).

Concern has been expressed about the possible long-term effects on the children of women who smoke during pregnancy. Butler (*6*) recently reported the results of a follow-up at age seven of the babies studied in the British Perinatal study of 1958. He found that the children of the mothers who were "heavy" smokers during pregnancy showed significantly decreased height, retardation of reading ability, and lower ratings on "social adjustment" than the children of nonsmoking mothers. The differences were independent of such factors as social class, age of mother, and parity.

EXPERIMENTAL STUDIES

In the past decade, research on the effect of smoking on pregnancy has increased. Summaries of human and animal experimental data in this area of study are found in tables 5 and 6. Elevated carbon monoxide levels have been found in maternal and fetal blood in women who smoke. Carbon monoxide is an inhibitor of carbonic anhydrase and as might be expected the activity of this enzyme is decreased in the cord blood of infants whose mothers smoke. The significance of elevated fetal carbon monoxide is not clear; however, in an extensive monograph on this subject, Longo, (*22*) has concluded that "... the decreased availability of oxygen resulting from elevated (fetal) carboxyhemoglobin levels is probably injurious to fetal tissues." Other changes noted in the infants of smoking mothers have included a mild metabolic acidosis and a higher mean hematocrit (*56*). Two studies (*9, 52*) have shown that placentas of women who smoke have a significantly greater ability to hydroxylate benzo[a]pyrene than the placentas from nonsmokers. Such findings suggest the possibility of fetal exposure to carcinogens; however, the significance of these findings is presently speculative.

Early animal studies (*10, 42*) showed that rats and rabbits exposed to nicotine or cigarette smoke have smaller offspring and more unsuccessful pregnancies than control animals. Recent radio-

TABLE 5.—*Human experimental data on smoking and pregnancy*

Author, year, country, reference	Design of study	Results	Comments
Sontag and Wallace, 1935, U.S.A. (*45*).	Fetal heart rate before and after smoking was studied 81 times in 5 patients.	Average fetal heart rate before smoking was 144.0. The average fetal heart rate for the eighth to the twelfth minute after starting to smoke was 149.0.	
Haddon et al., 1961, U.S.A. (*14*).	Carbon monoxide levels were measured in 50 smokers and nonsmokers in a prenatal clinic. Twenty-six paired maternal and umbilical vein blood specimens were obtained at parturition and tested for CO levels.	(*a*) Carbon monoxide levels were significantly ($p \leq 0.01$) higher in smokers than in nonsmokers. (*b*) Carbon monoxide concentrations in paired cord and maternal blood specimens were approximately equal. (*c*) O_2 carrying capacity in cord and maternal blood was reduced in smokers compared to nonsmokers.	
Heron, 1962, New Zealand (*15*).	58 pregnant smoking women were studied during labor to determine the effect which smoking might have on the "grading" of the infant at birth. CO levels were measured in both mother and fetus.	(*a*) CO levels in maternal and fetal blood were higher in patients who smoked. (*b*) Respirations in infants of mothers who smoked took longer to be established and peripheral cyanosis was more common.	A control group who had never smoked was compared with the survey group.
Kumar and Zourlas, 1963, U.S.A. (*20*).	The *in vivo* effects of cigarette smoking on uterine activity were studied in 17 pregnant gravidas near term and not in labor. The *in vitro* effect of nicotine on human pregnant and nonpregnant myometrial strips was studied.	(*a*) In more than half (10/17), a definite increment in uterine activity was noticed during cigarette smoking. (*b*) No oxytocic effect of nicotine on myometrial strips was noted.	
Young and Pugh 1963, England (*55*).	Blood CO levels were studied in 19 full-term parturient women, 16 of whom had normal deliveries. Six of these smoked 10 to 20 cigarettes a day. Maternal blood was analyzed 15 to 30 minutes prior to delivery. Fetal blood was taken from the placental end of the umbilical vein.	CO content of umbilical vein blood at normal deliveries was .52 and .36 volumes percent in infants of mothers who smoked and mothers who did not smoke, as compared with .33 and .28 volumes percent, respectively, in the maternal venous blood.	Blood CO levels were also studied in nonsmoking male laboratory workers in London and in males in Antarctica.

TABLE 5.—*Human experimental data on smoking and pregnancy (cont.)*

Author, year, country, reference	Design of study	Results	Comments
Mantell, 1964, New Zealand (*25*).	Cord bloods from 50 smokers and 50 nonsmokers were analyzed for carbonic anhydrase activity.	A decrease in carbonic anhydrase activity in the cord bloods of infants whose mothers smoked was noted.	Carbon monoxide is an inhibitor of carbonic anhydrase.
Scoppetta, 1968, Italy (*43*).	CO concentrations were measured in the venous blood of 46 pregnant women, including smokers and nonsmokers. Funicular venous blood was analyzed at the time of delivery.	CO levels were higher in smokers than in nonsmokers. CO concentrations were approximately the same in maternal and funicular venous blood.	
Younoszai et al., 1968, Canada (*56*).	32 women with normal pregnancies were studied of whom 16 smoked >20 cigarettes a day. Both groups of women had normal deliveries and healthy infants. Biochemical changes in the first 48 hours of life were studied in the infants.	(*a*) Mean CO saturation of Hb in the venous blood of the cigarette smoking mothers at the time of delivery was 8.3 percent and in the nonsmoking mothers 1.2 percent. The corresponding mean umbilical vein blood levels were 7.3 percent and .7 percent. (*b*) The blood Ph, pCO_2, and bicarbonate and lactate values in both groups of infants were within normal limits. (*c*) The infants of smoking mothers showed a higher mean hematocrit and mild metabolic acidosis.	
Engel et al., 1969, U.S.A. (*9*).	37 experiments were performed on placental blood samples obtained from 15 pregnancies to determine relative affinity of human fetal Hb for CO and O_2.	Human placental blood has a lower relative affinity for CO than adult blood. It was calculated that the affinity constant of fetal Hb was approximately 20 percent less than that of Hb A.	

TABLE 5.—*Human experimental data on smoking and pregnancy (cont.)*

Author, year, country, reference	Design of study	Results	Comments
Nebert et al., 1969, U.S.A. (*31*).	Aryl hydrocarbon hydroxylase activity was determined in the placentas obtained from 97 women at the time of childbirth; 46 of the women smoked between 20 and 40 cigarettes per day during pregnancy and 51 women were nonsmokers.	Significantly higher ($p<0.001$) levels of aryl hydrocarbon hydroxylase were found in women with a history of cigarette smoking.	
Welch et al., 1969, U.S.A. (*52*).	Benzpyrene hydroxylase and aminoazo dye: N-demethylase activity was measured in 17 human placentas obtained after childbirth from smokers and in 17 human placentas obtained from nonsmokers.	Enzymes were found in the placentas from all 17 smokers. No detectable activity was observed in the placentas of nonsmokers.	

TABLE 6.—*Animal experimental data on the effect of smoking and nicotine on pregnancy*

Author, year, country, reference	Animal	Design of study	Results	Comments
Essenberg et al., 1940, U.S.A. (*10*).	Albino rat.	393 "young" from pregnant rats exposed to tobacco smoke and 113 young from pregnant rats which received parenteral nicotine were studied.	The young of treated mothers were underweight; the young from nicotine injected mothers were more underweight than those from smoked mothers. Increased fetal wastage and neonatal deaths were observed in treated animals as compared to controls.	113 "young" served as controls.
Schoeneck, 1941, U.S.A. (*42*).	Rabbit.	Smoke from one cigarette was blown into the nostril of healthy does by means of a catheter each day. The does were "smoked" daily throughout pregnancy and lactation. 170 young from 28 litters of 7 "smoked" does were studied. The offspring were not subjected to smoking at any time.	(*a*) Offspring from "smoked" female rabbits were smaller at birth than controls (17 percent). (*b*) The stillbirth rate was 10 times as great in the "smoked" group. (*c*) The mortality rate was greater in the offspring of the "smoked" does.	Litters from the previous generation served as controls.
Nishimura and Nakai, 1958, Japan (*32*).	Mouse.	230 pregnant mice were injected, parenterally, with nicotine. Animals were sacrificed at term and mid-pregnancy to investigate the state of the pregnancy and the development of the offspring.	Nicotine had a lethal effect upon mice embryos and also had a teratogenic effect on their skeletal systems.	225 full-term fetuses removed from 29 untreated mice were used as controls.
Gatling, 1964, U.S.A. (*13*).	Chick embryo.	Chicken embryos were treated with doses of nicotine varying from 12 μg. to 1,000 μg. The effects of phenothiazines, corticosteroids, and catecholamines were also studied.	Nicotine induced cephalic hematoma formation and central nervous system depression.	

TABLE 6.—*Animal experimental data on the effect of smoking and nicotine on pregnancy (cont.)*

Author, year, country, reference	Animal	Design of study	Results	Comments
Becker and King, 1966, U.S.A. (*2*).	Rat.	100 primipara pregnant rats received a single heavy subcutaneous injection of nicotine on the 21st day of pregnancy, one day prior to expected term delivery. Fetal wastage, weight of newborns, neonatal deaths, and pregnant animals' responses were noted.	(*a*) Mortality was greater among pregnant rats than among controls. (*b*) Pregnant rats showed more marked hyperventilation and less body temperature depression than controls. (*c*) Delivery was delayed 2 to 4 days. (*d*) The young weighed less than normal and survived "poorly" during the first 48 hours of life	100 nonpregnant rats served as controls.
King and Becker, 1966, U.S.A. (*17*).	Rat.	Pregnant and nonpregnant rats were injected subcutaneously with heavy doses of a 2 percent solution of pure nicotine for the purpose of determining the LD_{50} for females of this strain (Osborne-Mendel). The LD_{50} for neonates of this strain was also determined within 6 to 24 hours of normal birth.	Osborne-Mendel rats LD_{50}: *mg./kg.* Pregnant adults ..... 27.4 Nonpregnant females ..... 33.5 Neonates ..... 14.55 Pregnant rats tended to die significantly later than nonpregnant rats, but their tolerance for nicotine was less.	
Mosier and Armstrong, 1967, U.S.A. (*27*).	Rat.	Alternate pregnant rats received oral nicotine in the dosage of either .05 mg./g. or .10 mg./g. of food. On the 20th day, the rats were killed and the fetuses were removed.	(*a*) On higher nicotine intake, there was lowering of food intake. (*b*) There was no change in fetal weight or length on either concentration. (*c*) There appeared to be no effect on the number of live and "absorbing" fetuses.	

TABLE 6.—*Animal experimental data on the effect of smoking and nicotine on pregnancy (cont.)*

Author, year, country, reference	Animal	Design of study	Results	Comments
Becker et al., 1968, U.S.A. (*8*).	Rat.	Controlled populations of pregnant rats were injected twice daily with doses of nicotine varying from .5 mg./kg. to 5 mg./kg. Effects on pregnant rats and newborn were studied.	(*a*) With the lower dosage of nicotine, the birthweights, survival, and developmental status did not differ from controls. (*b*) With thhe higher dosage, pregnant rats consumed less food and gained less weight than control mothers. Delivery dates were prolonged 2 to 4 days or more. Young were underweight and fetal in appearance. There were no abortions and no premature young.	Control rats were injected with saline.
Tjälve et al., 1968, Sweden (*48*).	Mouse.	The passage of ^{14}C-nicotine and its metabolites from the mother into the fetuses was studied.	(*a*) Nicotine and its metabolites accumulated in the placenta and passed into the fetus. (*b*) The metabolites present in the fetus originated from the mother. (*c*) The passage of nicotine into the fetus was the same during the last four days of pregnancy.	
Fabro and Sieber, 1969, U.S.A. (*11*).	Rabbit.	(1-methyl-^{14}C)-caffeine and G-(^{3}H)-nicotine were given to 6-day pregnant rabbits. The dose for nicotine was 50 μg./kg., intravenous, producing plasma levels similar to those attained in man by cigarette smoking (.06–.09 μg./ml.).	(*a*) One hour after (^{3}H)-nicotine treatment, a high level of radioactivity compared with that in maternal plasma was found in uterine secretion (ratio = 10.8). (*b*) Unchanged radioactive nicotine and some of its metabolites were present in the preimplantation blastocyst (blastocyst/plasma ratio $\simeq$ 3).	Radioactivity in uterine secretion was not found in nonpregnant controls.

TABLE 6.—*Animal experimental data on the effect of smoking and nicotine on pregnancy (cont.)*

Author, year, country, reference	Animal	Design of study	Results	Comments
Welch et al., 1969, U.S.A. (*52*).	Rat.	Rats which were pregnant for 18 days were given 40 mg./kg. of 3,4-benzpyrene; 1,2-benzanthracene; 1,2,5,6-dibenzanthracene; chrysene; 3,4-benzofluorene; anthracene; pyrene; fluoranthene; perylene; or phenanthrene orally, and BP-hydroxylase activity in the placenta was measured 24 hours later.	All compounds tested stimulated: BP-hydroxylase activity in the placenta. 1,2-benzanthracene was the most active inducer of BP-hydroxylase.	Placenta from control rats possessed very low BP-hydroxylase activity.
Younoszai et al., 1969, Canada (*57*).	Rat.	Pregnant rats were exposed to smoke from regular tobacco cigarettes, non-nicotine cigarettes made with lettuce leaves, and non-nicotine cigarettes (lettuce leaves) to which 15 mg. of nicotine was added. The rats were forced to inhale cigarette smoke by placing their cages in a smoking chamber. CO levels were maintained between 2 and 8 percent by exposing the animals to smoke 5 times a day at 2-hour intervals. Other groups of rats were fed restricted diets, receiving from 55 to 80 percent of the food consumed by control rats.	(*a*) Fetuses of all smoked rats were growth retarded compared to control animals, those exposed to tobacco smoke (cigarette) being most severely affected. (*b*) The amount of food consumed by rats exposed to cigarette smoke was reduced. (*c*) There was a significant direct relation between fetal body weight and the average amount of food eaten during pregnancy. (*d*) Fetal weight was reduced in prpportion to the decrease in maternal food intake in the two groups of rats exposed to the lettuce leaf cigarette smoke. In rats exposed to tobacco cigarettes, fetal weight was reduced more than expected from the decrease in maternal food intake.	Control rats were handled in the same way except that they were not exposed to cigarette smoke.
Canada (*51*). Kirschbaum et al., 1970, U.S.A. (*18*).	Sheep.	Intravenous injection of fresh solutions of nicotine, and simulated smoking of cigarettes. were carried out upon pregnant ewes. Cardiovascular functions, including gaseous exchange and blood flow of both the ewes and their fetuses were studied for acute effects.	No significant changes were observed as a result of either nicotine administration or smoke inhalation.	Each experiment included a control period during which attainment of a steady state was the aim.

isotope studies in mice (*48*) have indicated that nicotine and its metabolites accumulate in the placenta and are passed into the fetus.

Many of the experimental studies were designed to determine the pathophysiology of the effect of maternal smoking on the fetus. The experimental conditions in the several studies varied greatly as did the results. No unified concept of the effect of maternal smoking on fetal growth or on the outcome of pregnancy can be derived from the presently available research.

SUMMARY

Maternal smoking during pregnancy exerts a retarding influence on fetal growth as manifested by decreased infant birthweight and an increased incidence of prematurity, defined by weight alone. There is strong evidence to support the view that smoking mothers have a significantly greater number of unsuccessful pregnancies due to stillbirth and neonatal death as compared to nonsmoking mothers. There is insufficient evidence to support a comparable statement for abortions. The recently published Second Report of the 1958 British Perinatal Mortality Survey, a carefully designed and controlled prospective study involving large numbers of patients, adds further support to these conclusions.

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CHAPTER 6

Peptic Ulcer

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Peptic Ulcer

It has been estimated that 10 to 12 percent of all people will suffer from peptic ulcer disease at some time in their lives (*17*). In the U.S.A. in 1967, there were 5,323 deaths from gastric ulcer and 4,502 deaths from duodenal ulcer (*22*). Several studies have documented an association between smoking and peptic ulcer disease, which is stronger for gastric ulcer than for duodenal ulcer.

Prospective studies indicate that male cigarette smokers have increased peptic ulcer mortality ratios (see table 1). Although a trend toward increased mortality from gastric ulcer is seen in cigar and/or pipe smokers, the data do not allow significant conclusions to be drawn. Similarly, no firm conclusions can be drawn about female smokers.

Retrospective studies have consistently shown smaller numbers of nonsmokers in the peptic ulcer groups than in matched control populations (tables 2 and 3).

Cigarette smoking has been shown to reduce the efficacy of antacid therapy in documented peptic disease (*3*) and to slow peptic ulcer healing (*7*). One study indicated that smokers who had undergone surgical treatment for their peptic disease had more major complications, including recurrence of peptic disease, than nonsmokers (*14*).

Numerous studies in both animals and man have been performed to investigate the effect of smoking or the administration of nicotine on the gastrointestinal tract. Studies of gastric secretion and motility in normal controls and in patients with peptic ulcer disease as well as in experimental animals have produced conflicting results (*4, 16, 18, 19, 20*).

SUMMARY

Cigarette smoking males have an increased prevalence of peptic ulcer disease and a greater peptic ulcer mortality ratio. These relationships are stronger for gastric ulcer than for duodenal ulcer. Smoking appears to reduce the effectiveness of standard peptic ulcer treatment and to slow the rate of ulcer healing.

TABLE 1.—*Smoking and peptic ulcer disease mortality*

(Numbers in parentheses represent actual number of deaths)

SM = Smokers NS = Nonsmokers G = Gastric D = Duodenal

Author, year, country, reference	Number and type of population	Data collection	Actual deaths SM	Actual deaths NS	Mortality ratios	Comments
Doll and Hill, 1964, Great Britain (*5, 6*).	41,000 male British physicians.	Questionnaire and follow-up of death certificate.	54		Cigarettes/day: †Peptic — NS 1.00; All cigarette 7.00; 1–14 gs. per day 2.33; 15–24 10.33; >25 7.33. Pipe/cigar: Gastric 4.00	† Total number of deaths were too small to allow separate examinations.
Hammond, 1966, U.S.A. (*11*).	440,558 males 35–84 years of age in 25 States.	Interviews by ACS volunteers	G–83	11	NS ..... 1.00 (11) 1.00 (22); SM (age 45–64) 2.95 (83) 2.86 (93); SM (age 65–79) 4.06 (83) 1.50 (93)	
Kahn, 1966, U.S.A. (*12*).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	G–78 .....12 D–119 25		NS ..... 1.00(12) 1.00(25); SM; All cigarette .... 4.13(39) 2.98(57); 1–9 ..... 3.95 (5) 2.30 (6); 10–20 ..... 2.77(13) 2.74(26); 21–39 ..... 5.45(15) 3.98(22); >39 .....11.57 (6) 2.89 (3). Pipe: 1.00(12) 1.00(25); 2.84 (4) 1.59 (5). Cigar: 1.00(12) 1.00(25); 2.90 (7) 1.58 (8).	
Weir and Dunn, 1970, U.S.A. (*23*).	68,153 males in various occupations in California.	Questionnaire and follow-up of death certificate.	44		NS ..... 1.00; All cigarette .... 0.53; ±10 ..... 1.00 0.40; ±20 ..... 1.67 0.59; ≧30 ..... 2.38 0.32	No deaths from gastric ulcer occurred in nonsmokers and risk of those smoking ±10/day was set at 1.00. NS included pipe, cigar, and ex-smokers.

TABLE 2.—*Methods used in retrospective and cross sectional studies of peptic ulcer and smoking*

Author, year, country, reference	Sex	Cases		Controls		Comments
		Number	Method of selection	Number	Method of selection	
Barnett, 1927, U.S.A. (*2*).	M	66 Gastric. 178 Duodenal	Patients admitted between 1913 and 1926. Only cases with complete smoking history selected.	500	Selected at random from the general admissions-males, 20–60 years of age.	1. Retrospective review records at Peter Bent Brigham Hospital. 2. Ulcer diagnosis probably well established.
Trowell, 1934, England (*21*).	M	50 Duodenal	Not stated	400	Selected at random from wards of a general hospital.	1. Interviewed by investigator. 2. Ulcer diagnosis confirmed by X-ray and/or surgery.
Allibone and Flint, 1958, England (*1*).	M and F	107	Consecutive admissions to hospital of patients with gastric and duodenal hemorrhage or perforation.	107	Matched by age, sex, and time of admission from acute general surgical emergency admissions.	Patients and controls interviewed by same observer.
Doll et al., 1958, England (*7*).	M and F	327 Gastric. 338 Duodenal.	Ulcer patients in Doll and Hill Lung Cancer Study plus additional patients in Central Middlesex Hospital.	1,143	Patients with non-ulcer diseases. Each case matched with 2 control patients of same sex, 5-year age group, and same type of place of residence. Male patients matched by social class.	1. Same interviewers and questionnaire in cases and controls. 2. Ulcer diagnosis probably well established.
Edwards et al., 1959, England (*8*).	M	1,737	Men aged 60 and over on 11 General Practioners' lists were examined and interviewed by these practitioners. Represents about 84 percent of all such men on these lists. (9 percent non-response due to death and/or untraced.)			Of 143 considered to have a peptic ulcer, 53 were confirmed by X-ray.

TABLE 2. *Methods used in retrospective and cross sectional studies of peptic ulcer and smoking (cont.)*

Author, year, country, reference	Sex	Number	Method of selection	Controls		Comments
				Number	Method of selection	
Kasanen and Forsström, 1966, Finland (*13*).	M	43 Gastric. 57 Duodenal.	Successive male admissions with peptic ulcer treated at medical clinic or outpatient department of University Hospital. Only patients under 65 years of age or those who had been working were included.	100	Successive men treated at medical clinic who had no gastrointestinal symptoms or signs of CHD.	A special questionnaire was used for the interview.
Gillies and Skyring, 1968, 1968, Australia (*9*).	M and F	100 Gastric. 50 Duodenal.	Patients with peptic ulcer were selected from hospital admissions in 1967.	150	Matched by age and sex from the same ward at the same time and with absence of signs or symptoms or past history of upper gastrointestinal disease.	Diagnosis well established with X-ray, gastroscopy, or surgery.
Gillies and Skyring, 1969, Australia (*10*).	M and F	10 Gastric. 48 Duodenal. 18 Uncertain location.	1,405 workers from a broadcasting company, a manufacturing company, and a bus company were interviewed for a history of peptic ulcer.	100 1,329	Two control groups: 1. 100 peptic ulcer patients previously reported by authors. 2. 1,329 workers without ulcer.	All information obtained by question card. All ulcers were proved by X-ray or surgery.
Monson, 1970, U.S.A. (*15*).	M and F	52 Gastric. 452 Duodenal. 139 Not specified.	643 physicians from Massachusetts who responded affirmatively to a questionnaire sent to them in 1967 asking how many had had a peptic ucer.	625	Controls were physicians without ulcer disease who were matched to ulcer patients by year of birth.	Diagnosis established by X-ray or surgery except for 46 "clinical" cases.

TABLE 3.—*Summary of results of retrospective and cross sectional studies of peptic ulcer and smoking*

Author, year, country, reference	Percent nonsmoker		Amount of tobacco used	
	Cases	Controls	Cases	Controls
Barnett, 1927, U.S.A. (*2*).	Total ..... 18.0 Gastric ..... 15.0 Duodenal 20.0	25.0		
Trowell, 1934, England (*21*).	Duodenal 8.0	17.0	Average number: Cigarettes .. 12.0 per day Pipe ..... 1.6 ounces per week	.....11.1 per day .. 2.15 ounces per week
Allibone and Flint, 1958, England (*1*).	38.0	54.0		
Doll et al., 1958, England (*7*).	Gastric: Males ..... 1.3 Females ... 51.1 Duodenal: Males ..... 2.1 Females ... 53.7	4.7 66.8 5.8 62.0	Gastric: *Percent smoking >25 cigarettes per day* Males ..... 10.6 Females .... 1.1 Duodenal: Males ..... 10.2 Females 1.9	11.3 1.1 12.7 1.9
Edwards et al., 1959, England (*8*).	*Percent of peptic ulcer by smoking category* Never smoked ..... 6.0 Formerly smoked ..... 6.7 Cigarettes: 1–9 per day ..... 9.4 10–19 per day ..... 9.8 >20 per day ..... 12.0 Pipe ..... 6.5 Pipe and cigarettes 8.5			

TABLE 3.—*Summary of results of retrospective and cross sectional studies of peptic ulcer and smoking (cont.)*

Author, year, country, reference	Percent nonsmoker		Amount of tobacco used		
	Cases	Controls		Cases	Controls
Kasanen and Forsstr5m, 1966, Finland (*13*).	"Peptic" 10.0	40.0	Cigarettes per day:		
			<10 ..... 10.0		7.0
			10–20 ..... 19.0		17.0
			20 ..... 42.0		26.0
			>20 ..... 19.0		10.0
Gillies and Skyring, 1968, Australia (*9*).	Gastric 18.0	44.0	Mean number cigarettes per day:		
	Duodenal 62.0	71.0	Gastric 23.3		17.1
			Duodenal .. 23.2		23.0
			Duration of smoking (years):		
			Gastric 30.2		28.0
			Duodenal .. 24.2		28.2
Gillies and Skyring, 1969, Australia (*10*).	Gastric 17.9	55.6			
	Duodenal 36.6				
Monson, 1970, U.S.A. (*15*).	Duodenal 32.1	46.7	Percent smoking >20 cigarettes per day		
	Gastric 19.2		Age:	*Gastric*	*Duodenal*
	Not Specified .. 43.2		20 ..... 38.8	27.3	30.1
			30 ..... 45.7	43.0	47.1
			45 ..... 60.2	49.5	46.9
			60 ..... 54.1	40.4	44.0

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CHAPTER 7

Tobacco Amblyopia

Contents

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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