

**The
Health Consequences
of Smoking**

A Report of the Surgeon General: 1971

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

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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 bio-mechanisms 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.

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The professional staff has had the assistance and advice of a number of experts in the scientific and technical fields, both in and outside of the government. Their contributions are gratefully acknowledged. Special thanks are due the following:

- ANDERSON, WILLIAM H., M.D.—Chief, Pulmonary Disease Section, University of Louisville School of Medicine, Louisville, Ky.
- ANTHONISEN, NICHOLAS, R., M.D.—Ph. D.—Associate Professor, Department of Experimental Medicine, McGill University, Montreal, Quebec, Canada.
- AUERBACH, OSCAR, M.D.—Senior Medical Investigator, VA Hospital, East Orange, N.J.
- AYRES, STEPHEN M., M.D.—Director, Saint Vincent's Hospital and Medical Center of New York, Cardiopulmonary Laboratory, New York, N.Y.
- BAKER, CARL, M.D.—Director, National Cancer Institute, National Institutes of Health, Bethesda, Md.
- BELLET, SAMUEL, M.D.—Director, Division of Cardiology, Philadelphia General Hospital, Philadelphia, Pa.
- BING, RICHARD J., M.D.—Professor of Medicine, California Institute of Technology, Pasadena, Calif.
- BOCK, FRED G., Ph. D.—Director, Orchard Park Laboratories, Roswell Park Memorial Institute, Orchard Park, N.Y.
- BOREN, HOLLIS, M.D.—Professor of Medicine, Marquette School of Medicine, Wood VA Hospital, Milwaukee, Wis.
- BOUTWELL, ROSWELL K., M.D.—Professor of Oncology, McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, Wis.
- COOPER, THEODORE, M.D.—Director, National Heart Institute, National Institutes of Health, Bethesda, Md.
- CORNFIELD, JEROME—Research Professor of Biostatistics, University of Pittsburgh Graduate School of Public Health, Biostatistics Project, Bethesda, Md.
- EARL, CHRISTOPHER J., M.D.—National Hospital, London, England.
- EPSTEIN, FREDERICK H., M.D.—Professor of Epidemiology, University of Michigan, School of Public Health, Ann Arbor, Mich.
- FALK, HANS L., Ph. D.—Associate Director for Laboratory Research, National Institute of Environmental Health Sciences, Research Triangle Park, N. C.
- FERRIS, BENJAMIN G., JR., M.D.—Professor, Department of Physiology, Harvard School of Public Health, Boston, Mass.

- FITZPATRICK, MARK J., M.D., M.P.H.—Obstetrician, Perinatal Biology and Infant Mortality, National Institute of Child Health and Human Development, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md.
- FRAZIER, TODD M.—Assistant Director, Harvard Center for Community Health and Medical Care, Harvard School of Public Health, Boston, Mass.
- GOLDSMITH, JOHN R., M.D.—Head, Environmental Epidemiology Unit, California State Department of Public Health, Berkeley, Calif.
- HANNA, MICHAEL G., JR., Ph. D.—Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tenn.
- HIGGINS, IAN T. T., M.D., M.R.C.P.—Professor, Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Mich.
- HOFFMANN, DIETRICH, Ph. D.—Division of Environmental Toxicology, American Health Foundation, New York, N.Y.
- ISRAEL, ROBERT A.—Director, Division of Vital Statistics, National Center for Health Statistics, U.S.P.H.S., U.S. Department of Health, Education and Welfare, Rockville, Md.
- KELLER, ANDREW Z., D.M.D., M.P.H.—Chief, Research in Geographic Epidemiology, Veterans Administration Central Office, Washington, D.C.
- KIRSNER, JOSEPH, M.D.—Professor of Medicine, University of Chicago School of Medicine, Chicago, Ill.
- KNOX, DAVID L., M.D.—Associate Professor, The Wilmer Ophthalmological Institute, The Johns Hopkins University School of Medicine, Baltimore, Md.
- KOLBYE, ALBERT C., JR., M.D., J.D.—Deputy Director, Bureau of Foods, Food and Drug Administration, U.S. Department of Health, Education and Welfare, Washington D.C.
- KOTIN, PAUL, M.D.—Director, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.
- KRUMHOLZ, RICHARD A., M.D.—Director, Institute of Respiratory Diseases, Kettering Medical Center, Kettering, Ohio.
- LIEBOW, AVERILL A., M.D.—Professor and Chairman, Department of Pathology, University of California at San Diego, La Jolla, Calif.
- LILIENFELD, ABRAHAM, M.D.—Professor and Chairman, Department of Chronic Diseases, Johns Hopkins School of Hygiene and Public Health, Baltimore, Md.
- MACMAHON, BRIAN, M.D.—Professor of Epidemiology, Harvard University School of Public Health, Boston, Mass.
- MCLEAN, ROSS, M.D.—Medical Consultant, Regional Medical Program of Texas, Austin, Tex.
- McMILLAN, GARDNER C., M.D.—Chief, Arteriosclerotic Disease Branch, National Heart and Lung Institute, National Institutes of Health, Bethesda, Md.
- MITCHELL, ROGER S., M.D.—Director, University of Colorado Medical Center, Webb-Waring Institute for Medical Research, Denver, Colo.
- MURPHY, EDMOND A., M.D., Sc. D.—Associate Professor of Medicine and Biostatistics, The Johns Hopkins Hospital, Baltimore, Md.
- PAFFENBARGER, RALPH S., JR., M.D.—Chief, Bureau of Adult Health and Chronic Diseases, California State Department of Public Health, Berkeley, Calif.
- PETERS, JOHN M., M.D.—Associate Professor of Occupational Medicine, Harvard University School of Public Health, Boston, Mass.
- PETERSON, WILLIAM F., M.D.—Chairman, Department of Obstetrics and Gynecology, Washington Hospital Center, Washington, D.C.
- PETTY, THOMAS L., M.D.—Associate Professor of Medicine, University of Colorado Medical Center, Denver, Colo.

- SAFFIOTTI, UMBERTO, M.D.—Associate Scientific Director for Carcinogenesis Etiology, National Cancer Institute, National Institutes of Health, Bethesda, Md.
- SCHUMAN, LEONARD M., M.D.—Professor and Head, Division of Epidemiology, University of Minnesota School of Public Health, Minneapolis, Minn.
- SHIMKIN, MICHAEL B., M.D.—Coordinator, Regional Medical Program, University of California at San Diego, La Jolla, Calif.
- STAMLER, JEREMIAH, M.D.—Executive Director, Chicago Board of Health, Health Research Foundation, Chicago, Ill.
- UNDERWOOD, PAUL B., JR., M.D.—Associate Professor, Department of Obstetrics and Gynecology, University of South Carolina Medical School, Charleston, S.C.
- VAN DUUREN, BENJAMIN L., M.D.—Professor of Environmental Medicine, Institute of Environmental Medicine, New York University Medical Center, New York, N.Y.
- VICTOR, MAURICE, M.D.—Professor of Neurology, Department of Neurology, Case Western Reserve, Cleveland, Ohio.
- WYNDER, ERNEST L., M.D.—President and Medical Director, American Health Foundation, New York, N.Y.

The following professional staff of the National Clearinghouse for Smoking and Health contributed to the preparation of this report: John H. Holbrook, M.D., Richard W. White, Robert S. Hutchings, Elaine Bratic, Annabel W. Hecht, Richard H. Amacher, Donald R. Shopland and Jennie M. Jennings.

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Contents

	Page
PREFACE	iii
ACKNOWLEDGMENTS	v
Chapter 1. Introduction	1
Chapter 2. Cardiovascular Diseases	15
Chapter 3. Chronic Obstructive Bronchopulmonary Disease	135
Chapter 4. Cancer	231
Chapter 5. Pregnancy	385
Chapter 6. Peptic Ulcer	419
Chapter 7. Tobacco Amblyopia	431

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 supply 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

Age	Male			Female		
	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-

Following 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 alpha₁-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

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.

INTRODUCTION REFERENCES

- (1) DOLL, R., HILL, A. B., Smoking and carcinoma of the lung. Preliminary report. *British Medical Journal* 2: 739-748, September 23, 1950.
- (2) HAMMOND, E. C., HORN, D. The relationship between human smoking habits and death rates. *Journal of the American Medical Association* 155: 1316-1328, August 7, 1954.
- (3) HORN, D. Address given at National Conference on Smoking and Health, San Diego, Calif., September 9-11, 1970. 13 pp.
- (4) LEVIN, M. L., GOLDSTEIN, H., GERHARDT, P. R. Cancer and tobacco smoking. A preliminary report. *Journal of the American Medical Association* 143(4): 336-338, May 27, 1950.
- (5) NATIONAL CENTER FOR HEALTH STATISTICS. Changes in cigarette smoking habits between 1955 and 1966. U.S. Department of Health, Education, and Welfare, April 1970. 33 pp.
- (6) SCHREK, R., BAKER, L. A., BALLARD, G. P., DOLGOFF, S. Tobacco smoking as an etiologic factor in disease. I. Cancer. *Cancer Research* 10: 49-58, 1950.
- (7) WYNDER, E. L., GRAHAM, E. A. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma. A study of six hundred and eighty four proved cases. *Journal of the American Medical Association* 143(4): 329-336, May 27, 1950.

CHAPTER 2

Cardiovascular Diseases

Contents

	<i>Page</i>
Introduction	21
Epidemiological Studies.....	38
Coronary Heart Disease Mortality	38
Coronary Heart Disease Morbidity	39
Retrospective Studies.....	40
The Interaction of Cigarette Smoking and Other CHD Risk Factors	40
Smoking and Serum Lipids	41
Smoking and Hypertension.....	41
Smoking and Physical Inactivity	41
Smoking and Obesity	43
Smoking and Electrocardiographic Abnormalities ..	47
Smoking and Heart Rate	47
The Effect of Cessation of Cigarette Smoking on Coronary Heart Disease.....	47
The Constitutional Hypothesis	48
Autopsy Studies Relating Smoking, Atherosclerosis, and Sudden CHD Death	52
Experimental Studies Concerning the Relationship of Coronary Heart Disease and Smoking	56
Cardiovascular Effects of Cigarette Smoke and Nicotine	56
Coronary Blood Flow	58
Cardiovascular Effects of Carbon Monoxide	59
Effects of Smoking on the Formation of Atherosclerotic Lesions	63
The Effect of Smoking on Serum Lipid Levels	65
The Effect of Smoking on Thrombosis	66
Other Areas of Investigation.....	66
Cerebrovascular Disease	66
Nonsyphilitic Aortic Aneurysm	67
Peripheral Arteriosclerosis	72
Experimental Evidence.....	73
Thromboangiitis Obliterans.....	73
Summary and Conclusions	74

Coronary Heart Disease	74
Cerebrovascular Disease	75
Nonsyphilitic Aortic Aneurysm	75
Peripheral Vascular Disease	75
References	75

FIGURES

1. National Cooperative Pooling Project, Inter-Society Commission for Heart Disease Resources	23
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	24
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	25
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. Peoples Gas Light and Coke Company Study, 1958-1962.....	43
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)	44

LIST OF TABLES

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

1. Sudden death and acute mortality with first major coronary episodes	23
2. Coronary heart disease mortality ratios related to smoking—prospective studies	26
3. Sudden death from coronary heart disease related to smoking.....	30
4. Coronary heart disease morbidity as related to smoking.....	32
5. Coronary heart disease morbidity as related to smoking—angina pectoris—prospective studies	37
A 6. Coronary heart disease morbidity and mortality—retrospective studies	93
A 7. Differences in serum lipids between smokers and non-smokers	98

LIST OF TABLES (CONT.)

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

	<i>Page</i>
A 8. Blood pressure differences between smokers and non-smokers	103
9. Death rates from coronary heart disease, by systolic blood pressure: ILWU mortality study, 1951-1961	42
10. Death rates from coronary heart disease, by diastolic blood pressure: ILWU mortality study, 1951-1961	42
11. Death rates from coronary heart disease, among hypertensives and nonhypertensives: ILWU mortality study, 1951-1961	42
12. Death rates from coronary heart disease among men without abnormalities related to cardiopulmonary diseases by weight classification in 1951: ILWU mortality study, 1951-1961	45
13. Death rates from coronary heart disease, by electrocardiographic findings in 1951: ILWU mortality study, 1951-1961	45
14. 1958 status with respect to heart rate, blood pressure, cigarette smoking, and ten-year mortality rates, by cause (1,329 men originally age 40-59 and free of definite coronary heart disease) Peoples Gas Company Study, 1958-1968.	45
15. The effect of the cessation of cigarette smoking on the incidence of CHD	46
16. Annual probability of death from coronary heart disease, in current and discontinued smokers, by age, maximum amount smoked, and age started smoking	46
A 17. Incidence of new coronary heart disease by smoking category and behavior type for men 39-49 years of age	105
A 18. Incidence of new coronary heart disease by smoking category and behavior type for men 50-59 years of age	106
19. Autopsy studies of atherosclerosis	53
A 20. Experiments concerning the effects of smoking and nicotine on animal cardiovascular function	107
A 21. Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans	113
A 22. Experiments concerning the effect of nicotine or smoking on catecholamine levels	119
A 23. Experiments concerning the atherogenic effect of nicotine administration	120

LIST OF TABLES (CONT.)

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

	<i>Page</i>
24. Experiments concerning the atherogenic effect of carbon monoxide exposure and hypoxia	64
A 25. Experiments concerning the effect of smoking and nicotine upon blood lipids (Human Studies)	123
A 25a. Experiments concerning the effect of smoking and nicotine upon blood lipids (Animal Studies)	127
A 26. Experiments concerning the effect of carbon monoxide exposure upon blood lipids	129
A 27. Smoking and thrombosis	130
28. Deaths from cerebrovascular disease related to smoking	68
29. Deaths from nonsyphilitic aortic aneurysm related to smoking—prospective studies	71
A 30. Experiments concerning the effect of nicotine and smoking upon the peripheral vascular system	133

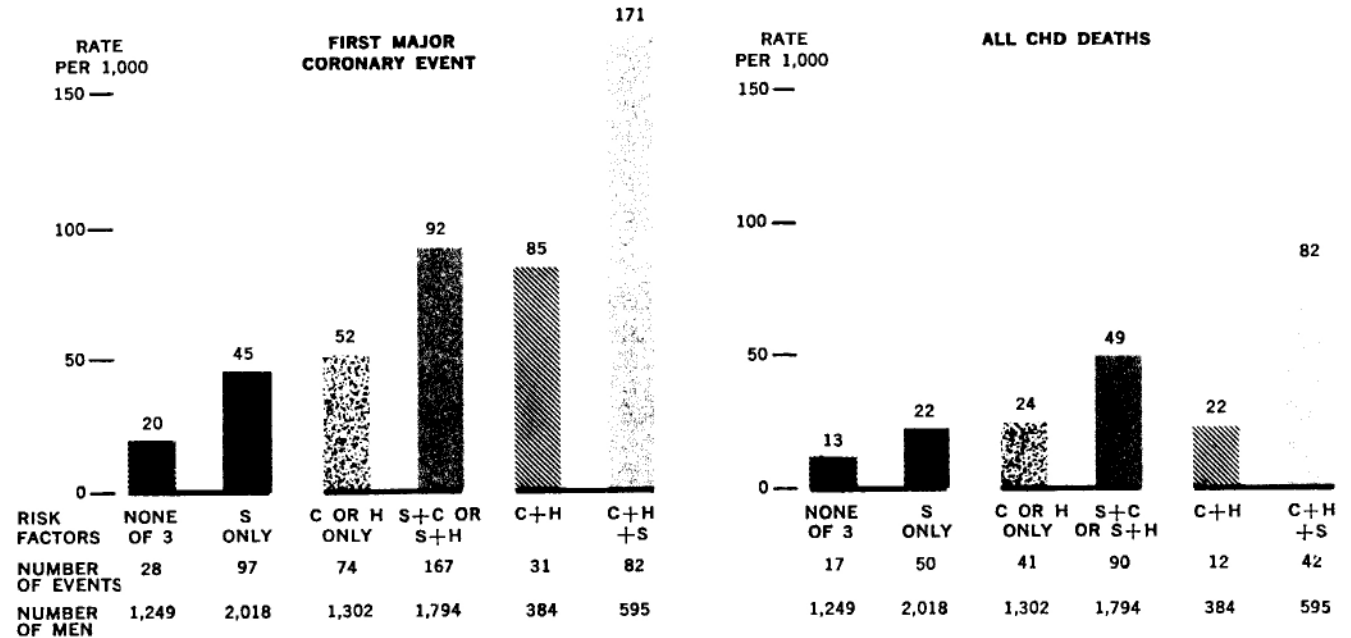
INTRODUCTION

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.

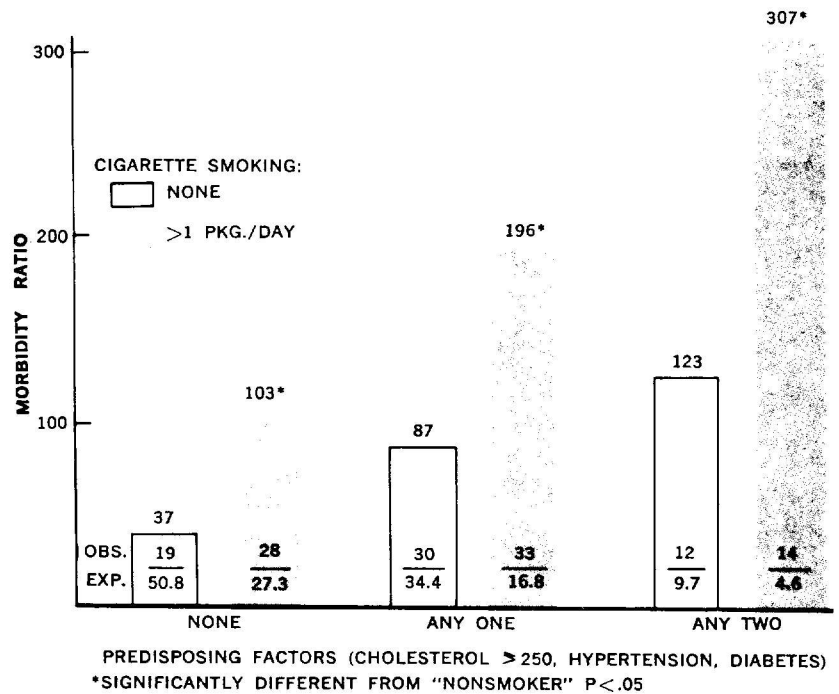


FIGURE 2—Risk of coronary heart disease (12 years) according to cigarette smoking habit and presence of "predisposing factors" (men 30-59 at entry). Framingham Heart Study.

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

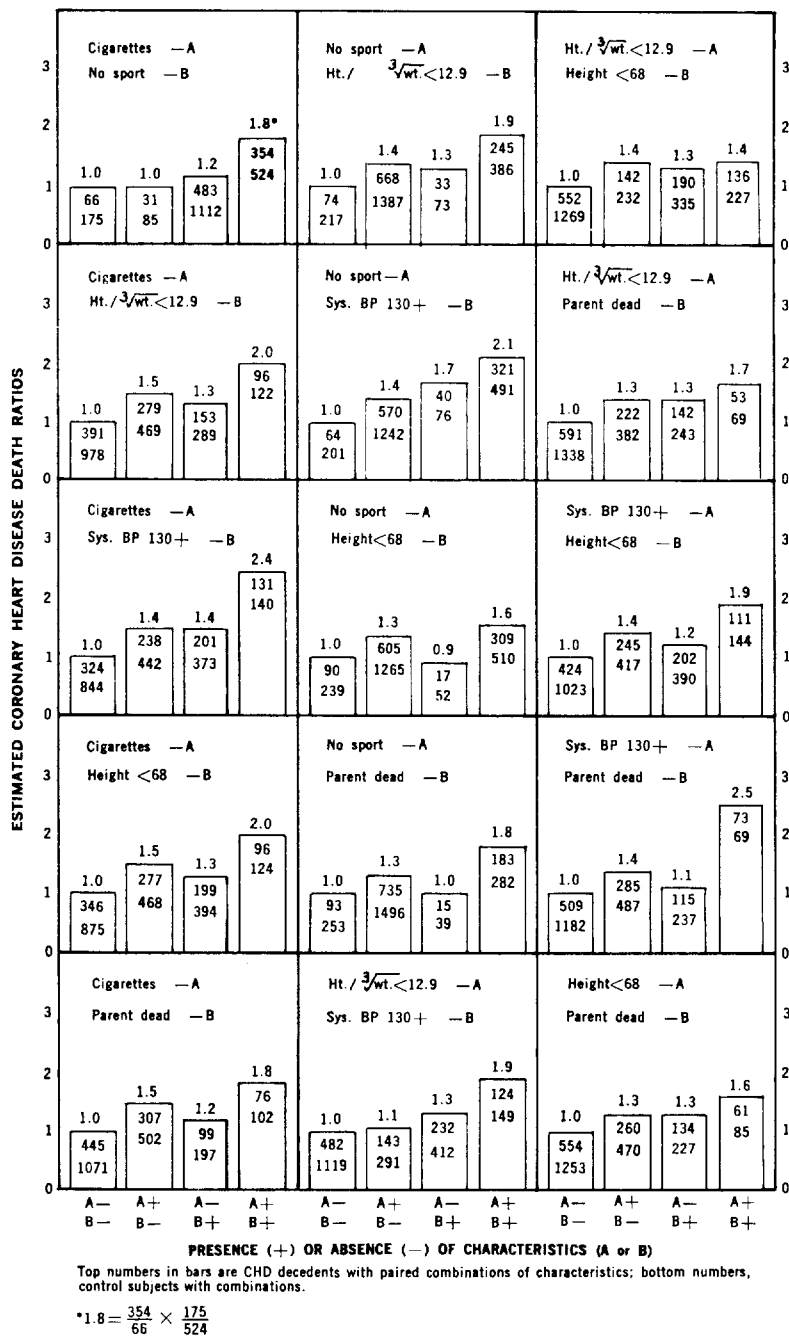


FIGURE 3—Estimated coronary heart disease death ratios in a 17–51 year follow-up, and frequencies of paired combinations of six high-risk characteristics in college, for all ages at death.

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	NS1.00 (709)
					All smokers .1.70 (3361) ² (p<0.001)
					<101.29 (192)
					10-201.89 (864)
					20-402.20 (604)
>402.41 (118)					
Doyle et al., 1964, U.S.A. (54).	2,282 males, Framingham, 30-62 years of age.	Detailed medical examination and follow-up.	10	93	NS1.00 (20)
					All smokers .2.40 (73)
					<202.00 (17)
					201.70 (20)
Doyle et al., 1964, U.S.A. (54).	1,913 males, Albany, 39-55 years of age.	Detailed medical examination and follow-up.	8	93	>203.50 (36)
Doll and Hill, 1964, Great Britain (50).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	1,376	NS1.00
					All smokers .1.35
					1-141.29
					15-241.27
>251.43					
Strobel and Gsell 1965 Switzerland (180).	3,749 male Swiss physicians.	Questionnaire and follow-up of death certificate.	9	162	NS1.00
					1-201.48
					>201.76
Best, 1966 Canada (24).	Approximately 78,000 male Canadian veterans.	Questionnaire and follow-up of death certificate.	6	2,000	NS1.00
					All smokers .1.60 (1380)
					<101.55 (337)
					10-201.58 (766)
>201.78 (277)					
Kahn 1966 U.S.A. (93).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	10,890	NS1.00 (2997)
					All smokers .1.74 (4150)
					1-91.39 (439)
					10-201.78 (2102)
					21-391.84 (1292)
>392.00 (266)					
Hirayama, 1967, Japan (84).	265,118 Japanese adults over age 40.	Trained interviewers and follow-up of death certificate.	1	91	NS1.00 (17)
					1-241.13 (69)
					>251.00 (5)
Kannel et al., 1968, U.S.A. (94).	5,127 males and females age 30-59.	Medical examination and follow-up.	12	52	NS1.00 (27) } (p<0.05)
					SM>202.20 (25) }

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

ratios related to smoking—prospective studies

shown in parentheses)¹

NS = Nonsmokers]

Cigars, pipes	Age variation				Comments
	50-54	55-59	60-64	65-69	
<i>Cigars</i>					
NS..1.00	NS1.00 (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)
<i>Pipes</i>					
NS..1.00	<101.38 (35)	1.38 (50)	1.17 (49)	1.27 (58)	
SM..1.03 (312)	10-202.00 (213)	2.04 (258)	1.91 (235)	1.58 (158)	
	>202.51 (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.
	NS1.00	1.00	1.00		
	1-143.73	1.40	1.71		
	15-244.45	1.73	1.27		
	>251.36	1.92	1.58		
NS..1.00					
SM..1.45					
<i>Cigars</i>					
NS..1.00	NS1.00	1.00	1.00		
SM..0.98 (16)	<100.97 (18)	1.56 (220)	1.71 (99)		
<i>Pipes</i>					
NS..1.00	10-201.45 (115)	1.67 (557)	1.29 (94)		
SM..0.96 (95)	>201.85 (65)	1.76 (184)	1.73 (28)		
<i>Cigars</i>					
NS..1.00					
SM..1.04 (623)					
<i>Pipes</i>					
NS..1.00					
SM..1.08 (886)					
					Preliminary report.

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

TABLE 2.—Coronary heart disease mortality ratios

(Actual number of deaths

[SM = Smokers

Author, year, country, reference	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day		
					Males	Females	
Hammond and Garfinkel, 1969, U.S.A. (76).	358,534 males	Questionnaire and follow-up of death certificate.	6	14,819	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	1.00	(385) (p<0.01)
					SM	1.50	
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 SM >20	1.00	(137)
						2.08	(154)
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	1.00	(4)
					<20	1.97	(20)
					>20	3.60	(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	1.00	
					All smokers	1.60	
					±10	1.39	
					±20	1.67	
					>30	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	1.00	(27)
					<10	1.65	(34)
					20	1.70	(86)
					>20	3.00	(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
	<i>Males</i>				†Based on 5-9 deaths.
	<i>40-49</i>	<i>50-59</i>	<i>60-69</i>	<i>70-79</i>	
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	
	<i>Females</i>				
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	—	
	<i>30-44</i>	<i>45-54</i>	<i>55-69</i>		
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.
	<i>35-44</i>	<i>45-54</i>	<i>55-64</i>	<i>65-69</i>	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. } 2.92 (6)
					< 5 cigars. }
					< 5 pipes. }
					10-19 cigarettes. } 3.67 (8)
					>20 cigarettes. } 3.83 (29)
					> 5 cigars. }
					> 5 pipes. }
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.	<i>Males</i> 40-59 NS 1.00 (1)
					EX 6.53 (10)
					Cigarettes 5.20 (36)
					<i>Females</i> NS 1.00 (21)
					EX 0.89 (3)
					Cigarettes 1.02 (14)

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

heart disease related to smoking

(of deaths shown in parentheses)

	Cigarettes/day	Cigars, pipes	Comment
Never smoked	1.00 (15)	1.00 (15)	See table 1 for description of Pooling Project.
10	1.90 (23)	1.36 (13)	
20	1.90 (50)		
>20	3.36 (44)		

morbidity as related to smoking

(manifestations shown in parentheses)¹

EX = Ex-smokers]

PROSPECTIVE STUDIES—Continued

	Pipes, cigars	Age variation	Comments
			Data include CHD deaths, only on males 40-49 years of age and free of CHD on entry. NS includes pipes, cigars, and ex-smokers.
			NS includes ex-smokers. Includes all CHD.
<i>Males—Continued</i>	<i>Males</i>		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)	
<i>Females—Continued</i>			
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 EX Current 0-15/day >16	1.00 (21) 2.47 (15) 2.78 (68) 1.39 (45) 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.	<i>Myocardial Infarction Males</i> NS All SM Heavy SM <i>Risk of CHD (overall) Males</i>	1.00 (21) 1.51 (153) 1.85 (59) 1.00 (61) 1.34 (25) 1.80 (90) 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.	NS All current cigarettes (p<0.01) <20 >20 >40	1.00 2.14 1.50 2.33 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	NS, EX (SM <20) All current (>20)	1.00 (305) 1.31 (103)
				†428 total.		

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

Myocardial infarction—Continued

Females

1.00 (31)

1.71 (23)

Risk of CHD (overall)—Continued

Females

1.00 (89)

0.86 (18)

1.29 (18)

0.93 (3)

Females	Males only	Males			Females			Total myo-
1.00	NS	35-44	45-54	55-64	35-44	45-54	55-64	cardial in-
2.00	SM	1.00	1.00	1.00	1.00	1.00	1.00	farction in-
(p>0.01)	(p<0.01)	2.47	3.06	1.69	2.25	2.87	1.80	cludes those
1.77		0.52	2.15	1.32	1.25	2.31	1.65	dead within
5.92		3.04	3.29	1.81	20.25	11.79	4.07	48 hours.
		10.09	7.69	5.30				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.	NS and EX	1.00 (62)
					All current	1.77 (150)
212 total.						
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.			<i>Coronary cases (87)</i>	
					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)				88 developed clinical coronary disease,
33				47 angina pectoris,
7				28 myocardial infarction,
11				13 deaths CHD.
12				
30				
2				
6				
(p<0.005)				

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

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

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

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

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

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day	Cigars and pipes	Age variation	Comments						
Doyle et al., 1964, U.S.A. (54).	2,282 males, Framingham, 30-62 years of age.	Detailed medical examination and follow-up.	10	81	NS	1.00 (30)		NS include ex-smokers and pipe and cigar smokers.						
					All	1.09 (51)								
					<20	1.17 (15)								
					20	0.99 (18)								
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)		NS include former pipe and cigar smokers.						
					All current cigarettes	1.44 (16)								
					>16	1.63 (14)								
Kannel et al., U.S.A. (94).	5,127 males and females 30-59 years of age	Medical examination and follow-up.	12	107	<i>Males</i>									
					NS	1.00 (16)								
					Heavy SM, >20 cigarettes	2.04 (17)								
					<i>Females</i>									
					NS	1.00 (53)								
					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	<i>Males</i>		<i>Males</i> NS...1.00 SM...1.71	<i>Males</i>			†(p<0.01) †(p<0.05) NS include ex-smokers.			
					NS	1.00		1.00	1.00	1.00		1.00		
					Current cigarettes	1.91		1.20	3.40	1.57		2.06		
					<40	1.51		1.20	<40	2.35		1.40	1.54	
					>40	4.85			>40	10.15		2.58	6.15	
										<i>Females</i>				
					NS	1.00		1.00	1.00	1.00		1.00		
					Current cigarettes	1.56		1.67	0.97	1.67		1.53	1.04	
					<40	1.67		1.53	1.04					
					>40	—		4.12	—					

¹Unless 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	² 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	² 46
	>100	369	163	954	147

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

² $p < 0.05$.

³ $p < 0.01$.

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

TABLE 11.—Death rates from coronary heart disease, among hypertensives and nonhypertensives: *ILWU mortality study, 1951-61*
 (Coronary heart disease as classified under ISC Code 420)

Age group	Blood pressure status ¹	Smokers		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).

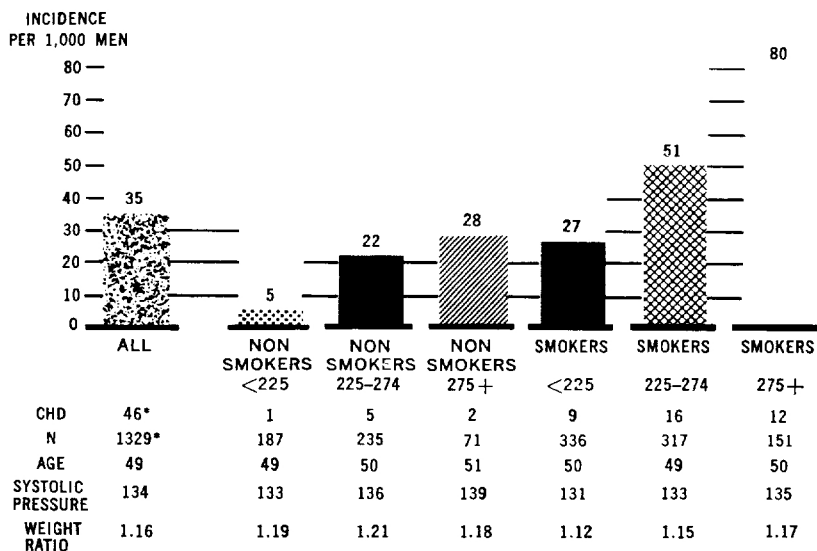


FIGURE 4—Relationship between smoking status and serum cholesterol level at initial examination, and incidence of clinical coronary heart disease in men originally age 40–59, free of definite CHD, and followed subsequently without systematic intervention, Peoples Gas Light and Coke Company study, 1958–1962.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

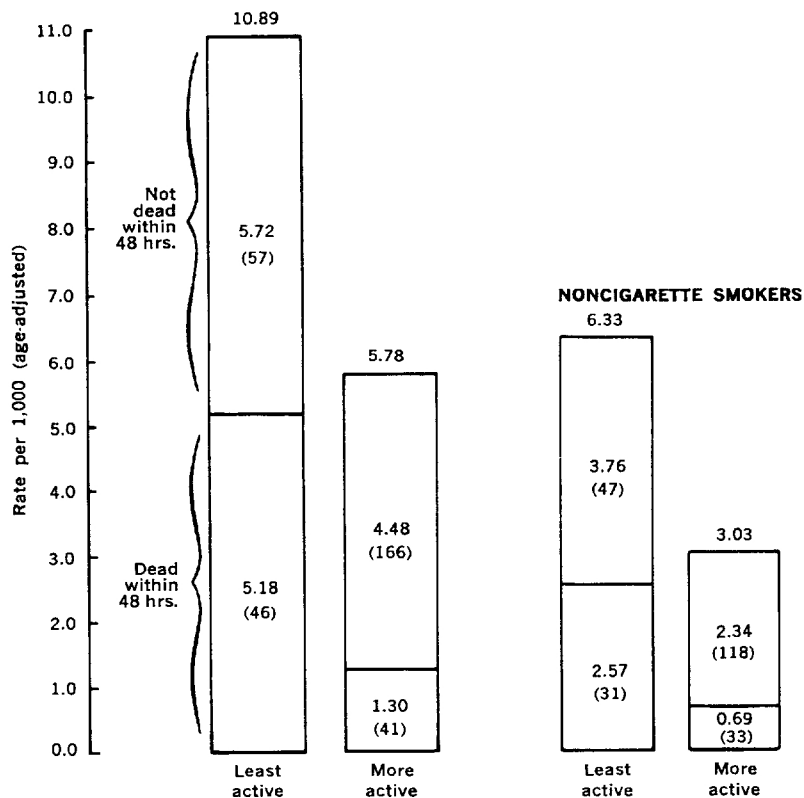
SOURCE: Stamler, J., et al. (177).

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			
Heart rate	Cigarette smoking	Diastolic pressure		All causes		CHD	
			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 ≥ 80 ; ≥ 10 cigarettes per day; diastolic blood pressure ≥ 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
Jenkins et al., 1968 U.S.A. (90).	<i>All CHD events</i>	
	Never smoked	1.00 (30)
	Current cigarette smokers	2.36 (84)
	Former cigarette smokers	2.15 (19)
	<i>All myocardial infarction</i>	
	Never smoked	1.00 (21)
	Current cigarette smokers	2.78 (68)
	Former cigarette smokers	2.47 (15)
	<i>Death from CHD</i>	
	<i>Smoked 1-19 cigarettes/day</i>	
Hammond and Garfinkel, 1969, U.S.A. (76).	Never smoked regularly	1.00 (1,841)
	Current cigarette smokers	1.90 (1,063)
	Stopped <1 year	1.62 (29)
	1-4	1.22 (57)
	5-9	1.26 (55)
	10-19	0.96 (52)
	>20	1.08 (70)
	All ex-cigarette smokers	1.16 (263)
	<i>Smoked >20 cigarettes/day</i>	
	Never smoked	1.00 (1,841)
	Current cigarette smokers	2.55 (2,822)
	Stopped <1 year	1.61 (62)
	1-4	1.51 (154)
	5-9	1.16 (135)
	10-19	1.25 (133)
	>20	1.05 (80)
	All ex-cigarette smokers	1.28 (564)
	<i>Total definite myocardial infarction</i>	
Shapiro et al., 1969, U.S.A. (172).	Never smoked	1.00
	Current cigarette smokers	1.87
	Stopped ≤5 years	0.76
	<i>All CHD deaths</i>	
Pooling Project, American Heart Association 1970, U.S.A. (88).	Never smoked	1.00 (27)
	>½ pack/day	1.65 (34)
	1 pack/day	1.70 (86)
	>1 pack/day	3.00 (68)
	Ex-smokers	0.80 (19)
	<i>First major coronary event</i>	
	Never smoked	1.00 (53)
	>½ pack/day	1.65 (72)
	1 pack/day	2.08 (205)
	>1 pack/day	3.28 (154)
	Ex-smokers	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	25-29	30-34
		Current smokers	Discontinued for five or more years (Probability × 10 ⁵)	Current smokers	Discontinued for five or more years
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

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.	<i>Severity of aortic sclerosis</i>				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.	
				<i>Above average</i>	<i>Average</i>	<i>Below average</i>			
			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						
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.	<i>Degree of coronary artery atherosclerosis (overall age-adjusted results)</i>				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.		
				<i>No atherosclerosis</i>	<i>Slight</i>	<i>Moderate</i>		<i>Advanced</i>	
			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					

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		
			Right coronary artery		Left coronary artery					
			SM	NS	SM	NS				
Avtandilov, 1965, Russia (18).	259 male and 141 female autopsies.	Not specified, but there were: 180 SM and 220 NS.	<i>Comparative size of mean area of atherosclerotic lesions in inner coat of coronary arteries.</i>				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-athero- sclerotic, 102-accidental, 202-various diseases. †T-test for significance of difference between means is significant at p<0.05 level.		
			<i>Right coronary artery</i>						<i>Left coronary artery</i>	
			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							
Sackett, et al., 1968, U.S.A. (165).	893 total, including 433 male and 450 female (white) patients autop- sied at Roswell Park Memorial Hospital. Represents all deaths 1956-1964 exclusive of 81 male pipe and cigar smokers and 55 incom- plete 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 athero- sclerosis occurred in the groups using either ciga- rettes only or both ciga- rettes 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 in- tensity 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 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 between 1963-1966 at Charity Hospital in New Orleans.	Interview with next of kin within 8 weeks of death.	<i>Basal Group (excluding diseases related to smoking or CHD). Mean percentage of coronary artery internal surface involved with raised lesions (number of cases).</i> <i>White</i> 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) <i>Negro</i> 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.

¹Unless 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 Yamamoto (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 Barger, 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 Rb⁸⁴ 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 pO₂ 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 O₂ 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 lipid deposition limited in penetration by the internal elastic membrane. Coronary vessels were found to show similar changes. Carboxyhemoglobin, (COHb) levels averaged 15-19 percent during the first 8 weeks and 33 percent during the final 2 weeks.
Kjeldsen et al., 1968, Denmark (117).	24 castrated male albino rabbits.	Regular diet plus 2 percent cholesterol: I. (12) control. II. (12) continual exposure to hypoxia: 10 percent O_2 for 6 weeks. 9 percent O_2 for 2 weeks.	The experimental group exposed to hypoxia showed increased macroscopic aortic atheromatosis over that shown by control animals. Microscopic examination revealed more intimal and subintimal lipid deposition in the aortas of the exposed rabbits than in those of the nonexposed. The total amount of cholesterol deposited in the aortas of the experimental group was three times higher than in those of the control group.
Kjeldsen et al., 1969, Denmark (114).	24 castrated male albino rabbits.	Regular diet plus 2 percent cholesterol: I. (12) control. II. (12) exposure to 28 percent O_2 for 10 weeks.	Macroscopically, the experimental group showed significantly fewer atheromatous changes. Microscopically, the experimental group showed significantly less aortic intimal lipid deposition.
Webster et al., 1970, U.S.A. (204).	22 female squirrel monkeys.	Diet containing 0.5 percent cholesterol and 25 percent fat: I. (10) control. II. (12) experimentally exposed to 200-300 p.p.m. carbon monoxide for 20 hours per week for 7 months.	The experimental group exposed to carbon monoxide showed a greater mean percentage of coronary arteries with atherosclerotic lesions and more lumen occlusion among the affected arteries. There were significantly more CO-treated monkeys than control monkeys having 35 percent or more apparent atherosclerotic stenosis among the affected arteries. Aortic atherosclerosis was apparently not aggravated by exposure to CO. COHb levels at the end of each exposure period averaged 16-26 percent during the final 24 weeks of the experiment.

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

THE EFFECT OF SMOKING ON SERUM LIPID LEVELS

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

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

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

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

THE EFFECT OF SMOKING ON THROMBOSIS

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

OTHER AREAS OF INVESTIGATION

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

CEREBROVASCULAR DISEASE

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

Epidemiological studies indicate that cigarette smoking is asso-

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

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

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

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

NON-SYPHILITIC AORTIC ANEURYSM

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

TABLE 28.—Deaths from cerebrovascular disease related to smoking

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

[SM = smokers NS = nonsmokers]

PROSPECTIVE STUDIES								
Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths due to CVD as underlying cause	Cigarettes per day	Pipes and cigars	Age variation	Comments
Hammond and Horn, 1958, U.S.A. (77, 78).	187,783 white males in 9 states 50-69 years of age.	Questionnaire and follow-up of death certificate.	3½	1,050	NS 1.00 (164)			†(p<0.01).
					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)								
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)			Data apply only to males 30-59 years of age at entry.
					Heavy SM (>20) 3.23 (8)			

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 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)	Pipes					
					All	SM 1.06 (82)					
					current	NS 1.00 (614)					
					Current		Cigars				
					cigarettes	NS 1.00 (614)					
					1-9	SM 1.08 (135)					
					10-20						
21-39											
>39											
Hammond and Garfinkel, 1969, U.S.A. (76).	358,534 males 445,875 females 40-79 years of age at entry.	Questionnaire and follow-up of death certificate.	6	4,099		Current regular cigarette	40-49	50-59	60-69	70-79	†Based on only 5-9 deaths.
					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	—	—		

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				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.
					Cases (158)	Controls (615)	
			SM	45.0	31.3 (p<0.01)		
		Cigarette SM >10 per day	20.9	11.2 (p<0.01)			

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	NS1.00 (25) (expected)			
					SM2.72 (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	NS1.00 (58)	NS ..1.00 (68)	NS ..1.00 (58)	
					Current cigarettes5.24 (234)	SM ..1.13 (8)	SM ..2.06 (24)	
					1-9 cigarettes/day ...2.12 (13)			
					10-205.53 (124)			
					21-395.95 (76)			
					>397.26 (17)			
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	NS1.00			Data apply only to males 50-69 years of age.
					1-92.62			
					10-193.85			
					20-394.54			
					>408.00			
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	NS1.00			SM include ex-smokers, NS include pipe and cigar smokers.
					All2.64			
					±102.44			
					±202.88			
					≧302.54			

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.

CARDIOVASCULAR REFERENCES

- (1) ACHESON, R. M., JESSOP, W. J. E. Tobacco smoking and serum lipids in old men. *British Medical Journal* 2: 1108-1111, October 28, 1961.
- (2) ADLER, I., HENSEL, O. Intravenous injections of nicotine and their effects upon the aorta of rabbits. *Journal of Medical Research* 15: 229-239, 1906.

- (3) ALLISON, R. D., ROTH, G. M. Central and peripheral vascular effects during cigarette smoking. *Archives of Environmental Health* 19(2): 189-198, August 1969.
- (4) AMBRUS, J. L., MINK, I. B. Effect of cigarette smoking on blood coagulation. *Clinical Pharmacology and Therapeutics* 5(4): 428-431, 1964.
- (5) ARONOW, W. S., KAPLAN, M. A., JACOB, D. Tobacco: A precipitating factor in angina pectoris. *Annals of Internal Medicine* 69(3): 529-536, September 1968.
- (6) ARONOW, W. S., SWANSON, A. J. Non-nicotinized cigarettes and angina pectoris. *Annals of Internal Medicine* 70(6): 1227, June 1969.
- (7) ARONOW, W. S., SWANSON, A. J. The effect of low-nicotine cigarettes on angina pectoris. *Annals of Internal Medicine* 71(3): 599-601, September 1969.
- (8) ASHBY, P., DALBY, A. M., MILLAR, J. H. D. Smoking and platelet stickiness. *Lancet* 2: 158-159, July 24, 1965.
- (9) ASTRUP, P. Effects of hypoxia and of carbon monoxide exposures on experimental atherosclerosis. *Annals of Internal Medicine* 71(2): 426-427, August 1969.
- (10) ASTRUP, P., KJELDSEN, K., WANSTRUP, J. Enhancing influence of carbon monoxide on the development of atheromatosis in cholesterol-fed rabbits. *Journal of Atherosclerosis Research* 7: 343-354, 1967.
- (11) ASTRUP, P., PAULI, H. G. (Editors). A Comparison of Prolonged Exposure to Carbon Monoxide and Hypoxia in Man. Reports of a Joint Danish-Swiss Study. *Scandinavian Journal of Clinical and Laboratory Investigation* 22 (Supplement 103): 1968. 71 pp.
- (12) AUERBACH, O., HAMMOND, E. C., GARFINKEL, L. Smoking in relation to atherosclerosis of the coronary arteries. *New England Journal of Medicine* 273(15): 775-779, October 7, 1965.
- (13) AVTANDILOV, G. G., KOLENOVA, V. I., PONOMARENKO, O. V. Kureniye tabaka i stepen' ateroskleroticheskogo porazheniya koronarnykh arteriy serdtsa i aorty. (Tobacco smoking and the degree of atherosclerotic lesions of coronary arteries of the heart and aorta.) *Kardiologiya* 5(1): 30-34, January-February 1965.
- (14) AYRES, S. M., GIANNELLI, S., JR., ARMSTRONG, R. G. Carboxyhemoglobin: Hemodynamic and respiratory responses to small concentrations. *Science* 149: 193-194, July 9, 1965.
- (15) AYRES, S. M., MUELLER, H. S., GREGORY, J. J., GIANNELLI, S., JR., PENNY, J. L. Systemic and myocardial hemodynamic responses to relatively small concentrations of carboxyhemoglobin (COHB). *Archives of Environmental Health* 18(4): 699-709, April 1969.
- (16) BALAZS, T., OHTAKE, S., CUMMINGS, J. R., NOBLE, J. F. Ventricular extrasystoles induced by epinephrine, nicotine, ethanol, and vasopressin in dogs with myocardial lesions. *Toxicology and Applied Pharmacology* 15(1): 189-205, July 1969.
- (17) BARGERON, L. M., JR., EHMKE, D., GONLUBOL, F., CASTELLANOS, A., SIEGEL, A., BING, R. J. Effect of cigarette smoking on coronary blood flow and myocardial metabolism. *Circulation* 15: 251-257, February 1957.
- (18) BARNETT, A. J., BOAKE, W. C. Cigarette smoking and occlusive arterial disease of the legs. *Medical Journal of Australia* 1: 240-242, February 13, 1960.
- (19) BEGG, T. B. Characteristics of men with intermittent claudication. *Practitioner* 194(2): 202-207, February 1965.

- (20) BELLET, S., FLEISCHMANN, D., ROMAN, L., DEGUZMAN, N. The effect of cigarette smoke inhalation on the ventricular fibrillation threshold. *Circulation (Supplement 3)* 42(4): 135, October 1970.
- (21) BELLET, S., KERSHBAUM, A., MEADE, R. H., JR., SCHWARTZ, L. The effect of tobacco smoke and nicotine on the normal heart and in the presence of myocardial damage produced by coronary ligation. *American Journal of the Medical Sciences* 201(1): 40-51, January 1941.
- (22) BELLET, S., WEST, J. W., MULLER, O. F., MANZOLI, U. C. Effect of nicotine on the coronary blood flow and related circulatory parameters. Correlative study in normal dogs and dogs with coronary insufficiency. *Circulation Research* 10(1): 27-34, January 1962.
- (23) BERKSON, D. M., STAMLER, J. LINDBERG, H. A., MILLER, W. A., STEVENS, E. L., SOYUGENIC, R., TOKICH, T. J., STAMLER, R. HEART rate: An important risk factor for coronary mortality—ten-year experience of the Peoples Gas Co. Epidemiologic study (1958-68). IN: Jones, R. J. (Editor). *Atherosclerosis. Proceedings of the Second International Symposium*. New York, Springer-Verlag, 1970. pp. 382-389.
- (24) BEST, E. W. R. *A Canadian Study of Smoking and Health*. Ottawa, Department of National Health and Welfare, 1966. 133 pp.
- (25) BLACKBURN, H., JR., ORMA, E., HARTEL G., PUNAR, S. Tobacco smoking and blood coagulation: Acute effect on plasma Stypven time. *American Journal of the Medical Sciences* 238: 448-451, October 1959.
- (26) BLOMSTRAND, R., LUNDMAN, T. Serum lipids, smoking and heredity. *Acta Medica Scandinavica* 180(Supplement 455): 51-60, 1966.
- (27) BORHANI, N. O., HECHTER, H. H., BRESLOW, L. Report of a 10-year followup study of the San Francisco longshoremen. Mortality from coronary heart disease and from all causes. *Journal of Chronic Diseases* 16: 1251-1266, 1963.
- (28) BOYLE, E., JR., MORALES, I. B., NICHAMAN, M. Z., TALBERT, C. R., JR., WATKINS, R. S. Serum beta lipoproteins and cholesterol in adult men. Relationships to smoking, age, and body weight. *Geriatrics* 23(12): 102-111, December 1968.
- (29) BREWER, G. J., EATON, J. W., WEIL, J. V., GROVER, R. F. Studies of red cell glycolysis and interactions with carbon monoxide, smoking, and altitude. *Advances in Experimental Medicine and Biology* 6: 95-114, 1970.
- (30) BRODY, J. S., COBURN, R. F. Carbon monoxide-induced arterial hypoxemia. *Science* 164(3885): 1297-1298, June 13, 1969.
- (31) BRONTE-STEWART, B. Cigarette smoking and ischaemic heart disease. *British Medical Journal* 1: 379-384, February 11, 1961.
- (32) BROWN, H., SELLWOOD, R. A., HARRISON, C. V., MARTIN, P. Thromboangiitis obliterans. *British Journal of Surgery* 56 (1): 59-63, January 1969.
- (33) BUECHLEY, R. W., DRAKE, R. M., BRESLOW, L. Relationship of amount of cigarette smoking to coronary heart disease mortality rates in men. *Circulation* 18(6): 1085-1090, December 1958.
- (34) BUNN, H. F., JANDL, J. H. Control of hemoglobin function within the red cell. *New England Journal of Medicine* 282(25): 1414-1421, June 18, 1970.
- (35) BURN, J. H., RAND, M. J. Action of nicotine on the heart. *British Medical Journal* 1: 137-139, January 18, 1958.
- (36) CAGANOVA, A., CAGAN, S., SIMKO, V. Lipidy krvneho sera u nefajciarov a fajciarov. (Blood serum lipids in nonsmokers and smokers.) *Bratislavské Lekárske Listy* 50(3): 387-392, September 3, 1968.

- (37) CEDERLOF, R. The Twin Method in Epidemiological Studies on Chronic Disease. Institute of Hygiene of the Karolinska Institute, Department of Environmental Hygiene of the National Institute of Public Health, Department of Sociology, University of Stockholm, Stockholm, 1966. 71 pp.
- (38) CEDERLOF, R., FRIBERG, L., HRUBEC, Z. Cardiovascular and respiratory symptoms in relation to tobacco smoking. A study on American twins. *Archives of Environmental Health* 18(6) : 934-940, June 1969.
- (39) CEDERLOF, R., FRIBERG, L., JONSSON, E., KAIJ, L. Respiratory symptoms and "angina pectoris" in twins with reference to smoking habits. An epidemiological study with mailed questionnaire. *Archives of Environmental Health* 13(6) : 726-737, December 1966.
- (40) CEDERLOF, R., JONSSON, E., LUNDMAN, T. On the validity of mailed questionnaires in diagnosing "angina pectoris" and "bronchitis". *Archives of Environmental Health* 13(6) : 738-742, December 1966.
- (41) CHEVALIER, R. B., KRUMHOLZ, R. A., ROSS, J. C. Reaction of non-smokers to carbon monoxide inhalation. Cardiopulmonary responses at rest and during exercise. *Journal of the American Medical Association* 198(10) : 1061-1064, December 5, 1966.
- (42) CHOI, Y. Y. Effect of nicotine upon cholesterol-induced atherosclerosis in rabbits. *New Medical Journal* 10(7) : 685-693, 1967.
- (43) CLARK, V. A., CHAPMAN, J. M., COULSON, A. H. Effects of various factors on systolic and diastolic blood pressure in the Los Angeles Heart Study. *Journal of Chronic Diseases* 20: 571-581, 1967.
- (44) COHEN, S. I., DEANE, M., GOLDSMITH, J. R. Carbon monoxide and survival from myocardial infarction. *Archives of Environmental Health* 19(10) : 510-517, October 1969.
- (45) CORNFIELD, J., MITCHELL, S. Selected risk factors in coronary disease. Possible intervention effects. *Archives of Environmental Health* 19(3) : 382-394, September 1969.
- (46) CZOCHRA-LYSANOWICZ, Z., GORSKI, M., KEDRA, M. Wpływ nikotyny i kofeiny na rozwój miażdżycy u królików. (The effect of nicotine and caffeine on the development of arteriosclerosis in rabbits.) *Annales Universitatis Mariae Curie-Skłodowska; Section D: Medicina* 14(20) : 181-206, 1959.
- (47) DAWBER, T. R., KANNEL, W. B., REVOTSKIE, N., STOKES, J., KAGAN, A., GORDON, T. Some factors associated with the development of coronary heart disease. Six years' followup experience in the Framingham study. *American Journal of Public Health and the Nation's Health* 49(10) : 1349-1356. October 1959.
- (48) DAYTON, S., PEARCE, M. L. Diet and atherosclerosis. *Lancet* 1(7644) : 473-474, February 28, 1970.
- (49) DAYTON, S., PEARCE, M. L., HASHIMOTO, S., DIXON, W. J., TOMIYASU, U. A Controlled Clinical Trial of a Diet High in Unsaturated Fat in Preventing Complications of Atherosclerosis. *Circulation* 40(1 Supplement 11), July 1969. 63 pp.
- (50) DOLL, R., HILL, A. B. Mortality in relation to smoking: 10 years' observations of British doctors. (Part I) *British Medical Journal* 1(5395) : 1399-1410, May 30, 1964.
- (51) DOLL, R., HILL, A. B. Mortality in relation to smoking: 10 years' observations of British doctors. (Concluded) *British Medical Journal* 1(5396) : 1460-1467, June 6, 1964.

- (52) DÖRKEN, H. Die Rauchgewohnheiten bei jüngeren Herzinfarkt-Patienten. (Smoking habits of younger patients with myocardial infarction.) Münchener medizinische Wochenschrift 109(4); 187-192 January 27, 1967.
- (53) DÖRKEN, H. Die Rauchgewohnheiten bei jüngeren Frauen mit Herzinfarkt. (The smoking habits of younger females with myocardial infarction.) Münchener medizinische Wochenschrift 109(41); 2129-2134, October 13, 1967.
- (54) DOYLE, J. T., DAWBER, T. R., KANNEL, W. B., KINCH, S. H., KAHN, H. A. The relationship of cigarette smoking to coronary heart disease. The second report of the combined experience of the Albany, N.Y., and Framingham, Mass., studies. Journal of the American Medical Association 190(10): 886-890, December 7, 1964.
- (55) DUNN, J. P., IPSEN, J., ELSOM, K. O., OHTANI, M. Risk factors in coronary artery disease, hypertension and diabetes. American Journal of the Medical Sciences 259(5): 309-322, May 1970.
- (56) EDWARDS, F., MCKEOWN, T., WHITFIELD, A. G. W. Association between smoking and disease in men over sixty. Lancet 1: 196-200, January 24, 1959.
- (57) EISEN, M. E. Coexistence of thromboangiitis obliterans and arteriosclerosis: Relationship to smoking. Journal of the American Geriatrics Society 14 (8): 846-858, August 1966.
- (58) ENGELBERG, H. Cigarette smoking and the *in vitro* thrombosis of human blood. Journal of the American Medical Association 193(12): 1033-1035, September 20, 1965.
- (59) ENGELBERG, H., FUTTERMAN, M. Cigarette smoking and thrombotic coagulation of human blood. Archives of Environmental Health 14(2): 266-270, February 1967.
- (60) ENGLISH, J. P., WILLIUS, F. A., BERKSON, J. Tobacco and coronary disease. Journal of the American Medical Association 115(16): 1327-1329, October 19, 1940.
- (61) EPSTEIN, F. H. Some uses of prospective observations in the Tecumseh Community Health Study. Proceedings of the Royal Society of Medicine 60(1): 4-8, January 1967.
- (62) FIDANZA, F., IMBIMBO, B., DI BENEDETTA, C. Indagine epidemiologica delle cardiopatie ischemiche nei reclusi del penitenziario di S. Stefano di Ventotene. (Epidemiological investigation of ischemic heart disease in prisoners of S. Stefano di Ventotene prison.) Giornale dell'Arteriosclerosi 4: 255-267 1966.
- (63) FLETCHER, C. M., HORN, D. Smoking and health. WHO Chronicle 24(8): 345-370, August 1970.
- (64) FOLLE, L. E., SAMANEK, M., AVIADO, D. M. Cardiopulmonary effects of tobacco and related substances. II. Coronary vascular effects of cigarette smoke and nicotine. Archives of Environmental Health 12(6): 712-716, June 1966.
- (65) FORTE, I. E., WILLIAMS, A. J., POTGIETER, L., SCHMITTHENNER, J. E., HAFKENSCHIEL, J. H., RIEGEL, C. Coronary blood flow and cardiac oxygen metabolism during nicotine-induced increases in left ventricular work. Annals of the New York Academy of Sciences 90(1): 174-185, September 27, 1960.
- (66) FRANKL, W. S., FRIEDMAN, R., SOLOFF, L. A. Cardiac output, blood pressure and free fatty acid responses to smoking in the nonbasal state. American Journal of the Medical Sciences 252(1): 39-44, July 1966.

- (67) FRANKL, W. S., WINTERS, W. L., SOLOFF, L. A. The effects of smoking on the cardiac output at rest and during exercise in patients with healed myocardial infarction. *Circulation* 31(1): 42-44, January 1965.
- (68) FREUND, J., WARD, C. The acute effect of cigarette smoking on the digital circulation in health and disease. *Annals of the New York Academy of Sciences* 90(1): 85-101, September 27, 1960.
- (69) FRIBERG, L., CEDERLOF, R., LUNDMAN, T., OLSSON, H. Mortality in smoking discordant monozygotic and dizygotic twins. A study on the Swedish Twin Registry. *Archives of Environmental Health* 21(4): 508-513, October 1970.
- (70) FRIEDEL, M. T. Effect of cigarette smoke on the peripheral vascular system. Radioactive iodinated albumin used as indicator of volumetric change. *Journal of the American Medical Association* 152(10): 897-900, July 4, 1953.
- (71) GLYNN, M. F., MUSTARD, J. F., BUCHANAN, M. R., MURPHY, E. A. Cigarette smoking and platelet aggregation. *Canadian Medical Association Journal* 95(11): 549-553, September 10, 1966.
- (72) GOFMAN, J. W., LINDGREN, F. T., STRISOWER, B., DELALLA, O., GLAZIER, F. TAMPLIN, A. Cigarette smoking, serum lipoproteins, and coronary heart disease. *Geriatrics* 10(8): 349-354, August 1955.
- (73) GOLDSMITH, J. R., LANDAW, S. A. Carbon monoxide and human health. *Science* 162(3860): 1352-1359, December 20, 1968.
- (74) GREENSPAN, K., EDMANDS, R. E., KNOEBEL, S. B., FISCH, C. Some effects of nicotine on cardiac automaticity, conduction, and inotropy. *Archives of Internal Medicine* 123(6): 707-712, June 1969.
- (75) GROSOGGEAT, Y., ANGUERA, G., LELLOUCH, J., JACOTOT, B., BEAUMONT, J.-L., PATOIS, E., MANIER, E. L'intoxication chronique par la nicotine chez le lapin nourri au cholestérol. Effets sur la paroi aortique et sur la lipémie. (Chronic nicotine poisoning in the rabbit on a cholesterol diet. Effects on the wall of the aorta and on lipidemia.) *Journal of Atherosclerosis Research* 5(3): 291-301, 1965.
- (76) HAMMOND, E. C., GARFINKEL, L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. *Archives of Environmental Health* 19(2): 167-182, August 1969.
- (77) HAMMOND, E. C., HORN, D. Smoking and death rates—report on forty-four months of follow-up of 187,783 men. I. Total mortality. *Journal of the American Medical Association* 166(10): 1159-1172, March 8, 1958.
- (78) HAMMOND, E. C., HORN, D. Smoking and death rates—report on forty-four months of follow-up of 187,783 men. II. Death rates by cause. *Journal of the American Medical Association* 166(11): 1294-1308, March 15, 1958.
- (79) HARLAN, W. R., OBERMAN, A., MITCHELL, R. E., GRAYBIEL, A. Constitutional and environmental factors related to serum lipid and lipoprotein levels. *Annals of Internal Medicine* 66(3): 540-555, March 1967.
- (80) HASS, G. M., LANDERHOLM, W., HEMMENS, A. Production of calcific athero-arteriosclerosis and thromboarteritis with nicotine, vitamin D, and dietary cholesterol. *American Journal of Pathology* 49(4): 739-771, October 1966.
- (81) HAUGE, M., HARVALD, B., REID, D. D. A twin study of the influence of smoking on morbidity and mortality. *Acta Geneticae Medicae et Gemellologiae* 19: 335-336, 1970.

- (82) HEYDEN-STUCKY, S., SCHIBLER-REICH, S. Kardiologische Risikofaktoren bei Schweizer Männern. (Cardiological risk factors in Swiss men.) Schweizerische Medizinische Wochenschrift 97(1): 20-25, January 7, 1967.
- (83) HIGGINS, M. W., KJELSBURG, M. Characteristics of smokers and non-smokers in Tecumseh, Michigan. II. The distribution of selected physical measurements and physiologic variables and the prevalence of certain diseases in smokers and nonsmokers. American Journal of Epidemiology 86(1): 60-77, July 1967.
- (84) HIRAYAMA, T. Smoking in relation to the death rates of 265,118 men and women in Japan. National Cancer Center, Research Institute. Tokyo, September 1967. 14 pp.
- (85) HOOD, B., TIBBLIN, G., WELIN, G., ORNDAHL, G., KORSAN-BENGTSEN, K. Myocardial infarction in early age. III. Coronary risk factors and their deficient control. Acta Medica Scandinavica 185(4): 241-251, April 1969.
- (86) HUEPER, W. C. Experimental studies in cardiovascular pathology. VII. Chronic nicotine poisoning in rats and in dogs. A.M.A. Archives of Pathology 35: 846-856, 1943.
- (87) HYAMS, L., SEGI, M., ARCHER, M. Myocardial infarction in the Japanese. A retrospective study. American Journal of Cardiology 20(4): 549-554, October 1967.
- (88) INTER-SOCIETY COMMISSION FOR HEART DISEASE RESOURCES. Atherosclerosis Study Group and Epidemiology Study Group. Primary prevention of the atherosclerotic diseases. Circulation 42(6): A-54-A-95, December 1970.
- (89) IRVING, D. W., YAMAMOTO, T. Cigarette smoking and cardiac output. British Heart Journal 25: 126-132, 1963.
- (90) JENKINS, C. D., ROSENMAN, R. H., ZYZANSKI, S. J. Cigarette smoking. Its relationship to coronary heart disease and related risk factors in the Western Collaborative Group Study. Circulation 38(6): 1140-1155, December 1968.
- (91) JOUVE, A., ROCHU, P., AVRIL, P. Enquetes epidemiologiques sur l'atherosclerose dans la region Provencale. (Epidemiological investigations of atherosclerosis in the Provence region.) Union Medicale du Canada 98(5): 761-766, May 1969.
- (92) JUERGENS, J. L., BARKER, N. W., HINES, E. A., JR. Arteriosclerosis obliterans: Review of 520 cases with special reference to pathogenic and prognostic factors. Circulation 21(2): 188-195, February 1960.
- (93) KAHN, H. A. The Dorn study of smoking and mortality among U.S. veterans: report on 8½ years of observation. IN: Haenszel, W. (Editor). Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966. pp. 1-125.
- (94) KANNEL, W. B., CASTELLI, W. P., MCNAMARA, P. M. Cigarette smoking and risk of coronary heart disease. Epidemiologic clues to pathogenesis. The Framingham study. IN: Wynder, E. L., Hoffmann, D., (Editors). Toward a Less Harmful Cigarette. Bethesda, U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute Monograph No. 28, June 1968. pp. 9-20.
- (95) KANNEL, W. B., DAWBER, T. R., SKINNER, J. J., JR., MCNAMARA, M., SHURTLEFF, D. Epidemiological aspects of intermittent claudication: The Framingham Study. Circulation (Supplement II to Vols. 31 and 32): 121-122, October 1965.

- (96) KANNEL, W. B., DAWBER, T. R., COHEN, M. E., MCNAMARA, P. M. Vascular disease of the brain—epidemiologic aspects. The Framingham study. *American Journal of Public Health and the Nation's Health* 55(9) : 1355-1366, September 1965.
- (97) KARVONEN, M., ORMA, E., KEYS, A., FIDANZA, F., BROXEK, J. Cigarette smoking, serum-cholesterol, blood-pressure, and body fatness. Observations in Finland. *Lancet* 1: 492-494, March 7, 1959.
- (98) KASTL, O. Berufliche und Umweltanalyse infarktkranker Eisenbahnbiensteter. (Occupational and environmental analysis of infarct patients in railway service.) *Medizinische Klinik* 64(42) : 1911-1917, October 17, 1969.
- (99) KEDRA, M., DOMOWSKI, G. The influence of tobacco smoking on the development of atherosclerosis and on the composition of blood lipids. *Polish Medical Journal* 5(1) : 37-43, 1966.
- (100) KEDRA, M., KOROLKO, A. Tobacco smoking and blood clotting. *Bulletin of Polish Medical Science and History* 8: 145-148, October 1965.
- (101) KEDRA, M., POLESZAK, J., PITERA, A. Wplyw palenia tytoniu na poziom tluszczowcow krwi. (Influence of tobacco smoking on the blood lipid levels.) *Polski Tygodnik Lekarski* 20(39) : 1452-1454, September 27, 1965.
- (102) KERRIGAN, R., JAIN, A. C., DOYLE, J. T. The circulatory response to cigarette smoking at rest and after exercise. *American Journal of the Medical Sciences* 255(2) : 113-119, February 1968.
- (103) KERSHBAUM, A., BELLET, S., CAPLAN, R. F., FEINBERG, L. J. Effect of cigarette smoking on free fatty acids in patients with healed myocardial infarction. *American Journal of Cardiology* 10(2) : 204-208, August 1962.
- (104) KERSHBAUM, A., BELLET, S., DICKSTEIN, E. R., FEINBERG, L. J. Effect of cigarette smoking and nicotine on serum free fatty acids. Based on a study in the human subject and the experimental animal. *Circulation Research* 9(3) : 631-638, May 1961.
- (105) KERSHBAUM, A., BELLET, S., HIRABAYASHI, M., FEINBERG, L. J. Regular filtertip, and modified cigarettes. Nicotine excretion, free fatty acid mobilization and catecholamine excretion. *Journal of the American Medical Association* 201(7) : 545-546, August 14, 1967.
- (106) KERSHBAUM, A., BELLET, S., JIMENEZ, J., FEINBERG, L. J. Differences in effects of cigar and cigarette smoking on free fatty acid mobilization and catecholamine excretion. *Journal of the American Medical Association* 195(13) : 1095-1098, March 28, 1966.
- (107) KERSHBAUM, A., BELLET, S., KHORSANDIAN, R. Elevation of serum cholesterol after administration of nicotine. *American Heart Journal* 69(2) : 206-210, February 1965.
- (108) KERSHBAUM, A., JIMENEZ, J., BELLET, S., ZANUTTINI, D. Modification of nicotine-induced hyperlipidemia by anti-adrenergic agents. *Journal of Atherosclerosis Research* 6: 524-530, 1966.
- (109) KERSHBAUM, A., KHORSANDIAN, R., CAPLAN, R. F., BELLET, S., FEINBERG, L. J. The role of catecholamines in the free fatty acid response of cigarette smoking. *Circulation* 28(1) : 52-57, July 1963.
- (110) KERSHBAUM, A., OSADA, H., SRIABINE, A., BELLET, S., PAPPAJOHN, D. J. Influence of nicotine on the mobilization of free fatty acids from rat adipose tissue *in vitro* and in the isolated perfused dog limb. *Circulation* 36(4, Supplement 2) : 20, October 1967.
- (111) KEYS, A. (Editor). *Coronary Heart Disease in Seven Countries*. *Circulation* 41(4, Supplement 1) : 1970. 211 pp.

- (112) KIEN, G. A., SHERROD, T. R. Action of nicotine and smoking on coronary circulation and myocardial oxygen utilization. *Annals of the New York Academy of Sciences* 90(1) : 161-173, September 27, 1960.
- (113) KJELDSSEN, K. Smoking and Atherosclerosis. Investigations on the significance of the carbon monoxide content in tobacco smoke in atherogenesis. Copenhagen, Munksgaard, 1969. 145 pp.
- (114) KJELDSSEN, K., ASTRUP, P., WANSTRUP, J. Reversal of rabbit atheromatosis by hyperoxia. *Journal of Atherosclerosis Research* 10(2) : 173-178, September-October 1969.
- (115) KJELDSSEN, K., DAMGAARD, F. Influence of prolonged carbon monoxide exposure and altitude hypoxia on serum lipids in man. *Scandinavian Journal of Clinical and Laboratory Investigation* 22 (Supplementum 103) : 16-19, 1968.
- (116) KJELDSSEN, K., MOZES, M. Buerger's disease in Israel. Investigations on carboxyhemoglobin and serum cholesterol levels after smoking. *Acta Chirurgica Scandinavica* 135(6) : 495-498, 1969.
- (117) KJELDSSEN, K., WANSTRUP, J., ASTRUP, P. Enhancing influence of arterial hypoxia on the development of atheromatosis in cholesterol-fed rabbits. *Journal of Atherosclerosis Research* 8(5) : 835-845, 1968.
- (118) KLENSCH, H. Blut-Katecholamine und -Fettsäuren beim Stress durch Rauchen und durch körperliche Arbeit. (Blood catecholamines and fatty acids under stress induced by smoke and exercise.) *Zeitschrift für Kreislaufforschung* 55(10) : 1035-1044, October 1966.
- (119) KONTTINEN, A. Cigarette smoking and serum lipids in young men. *British Medical Journal* 1: 1115-1116, April 21, 1962.
- (120) KONTTINEN, A., RAJASALMI, M. Effect of heavy cigarette smoking on post-prandial triglycerides, free fatty acids, and cholesterol. *British Medical Journal* 1(5334) : 850-852, March 30, 1963.
- (121) KRUMHOLZ, R. A., CHEVALIER, R. B., ROSS, J. C. Cardiopulmonary function in young smokers. A comparison of pulmonary function measurements and some cardiopulmonary responses to exercise between a group of young smokers and a comparable group of nonsmokers. *Annals of Internal Medicine* 60(4) : 603-610, April 1964.
- (122) KRUMHOLZ, R. A., CHEVALIER, R. B., ROSS, J. C. Changes in cardiopulmonary functions related to abstinence from smoking. Studies in young cigarette smokers at rest and exercise at 3 and 6 weeks of abstinence. *Annals of Internal Medicine* 62(2) : 197-207, February 1965.
- (123) KUHN, R. A. Mode of action of tobacco smoke inhalation upon the cerebral circulation. *Annals of the New York Academy of Sciences* 142 (Article 1) : 67-71, March 15, 1967.
- (124) LARSON, R. K., FUKUDA, P., MURRAY, J. F. Systemic and pulmonary vascular effects of nicotine in anesthetized dogs. *American Review of Respiratory Diseases* 91(4) : 556-564, April 1965.
- (125) LEADERS, F. E., LONG, J. P. Action of nicotine on coronary vascular resistance in dogs. *American Journal of Physiology* 203(4) : 621-625, October 1962.
- (126) LEB, G., DERNTL, F., ROBIN, E., BING, R. J. The effect of nicotine on effective and total coronary blood flow in the anesthetized closed-chest dog. *Journal of Pharmacology and Experimental Therapeutics* 173(1) : 138-144, May 1970.
- (127) LILIENTHAL, J. L., JR. Carbon monoxide. *Pharmacological Review* 2: 324-354, 1950.

- (128) MCKUSICK, V. A., HARRIS, W. S., OTTESEN, O. E., GOODMAN, R. M., SHELLEY, W. M., BLOODWELL, R. D. Buerger's disease: A distinct clinical and pathologic entity. *Journal of the American Medical Association* 181(1) : 5-12, July 7, 1962.
- (129) MARSHALL, W. J., JR., STANLEY, E. L., KEZDI, P. Cardiovascular effects of cold pressor tests, 40° head-up tilt, and smoking on smokers and nonsmokers. *Diseases of the Chest* 56(4) : 290-296, October 1969.
- (130) MASLOVA, K. K. The influence of nicotine on experimental atherosclerosis. *Bulletin of Experimental Biology and Medicine* 41 : 20-23, 1956.
- (131) MILLS, C. A., PORTER, M. M. Tobacco smoking and automobile-driving stress in relation to deaths from cardiac and vascular causes. *American Journal of the Medical Sciences* 234(1) : 35-43, July 1957.
- (132) MIYAZAKI, M. Circulatory effect of cigarette smoking, with special reference to the effect on cerebral hemodynamics. *Japanese Circulation Journal* 33(9) : 907-912, September 1969.
- (133) MODZELEWSKI, A., MALEC, A. Zachowanie się niektórych lipidów we krwi u palaczy. (Patterns of certain blood lipids in smokers.) *Wiadomości Lekarskie* 22(3) : 229-233, February 1, 1969.
- (134) MOYER, C. A., MADDOCK, W. G. Peripheral vasospasm from tobacco. *A.M.A. Archives of Surgery* 49(2) : 277-285, February 1940.
- (135) MULCAHY, R., HICKEY, N. J. Cigarette smoking habits of patients with coronary heart disease. *British Heart Journal* 28 : 404-408, 1966.
- (136) MULCAHY, R., HICKEY, N. J. The role of cigarette smoking in the causation of atherosclerosis. *Geriatrics* 22(2) : 165-174, February 1967.
- (137) MULCAHY, R., HICKEY, N. J., MAURER, B. J. Coronary heart disease in women. Study of risk factors in 100 patients less than 60 years of age. *Circulation* 36(4) : 577-586, October 1967.
- (138) MULINOS, M. G., SHULMAN, I. The effects of cigarette smoking and deep breathing on the peripheral vascular system. Studied by five methods. *American Journal of the Medical Sciences* 199(5) : 708-720, May 1940.
- (139) MURCHISON, L. E., FYFE, T. Effects of cigarette smoking on serum lipids, blood-glucose, and platelet adhesiveness. *Lancet* 2(7456) : 182-184, July 23, 1966.
- (140) MURPHY, E. A. Thrombozyten, Thrombose und Gerinnung, (Thrombocytes, thrombosis and clotting.) IN: Schievelbein, H. (Editor). *Nikotin: Pharmakologie und Toxikologie des Tabakrauches*. Stuttgart (West Germany), Georg Thieme Verlag, 1968. pp. 178-192.
- (141) MUSTARD, J. F., MURPHY, E. A. Effect of smoking on blood coagulation and platelet survival in man. *British Medical Journal* 1(5334) : 846-849, March 30, 1963.
- (142) NADEAU, R. A., JAMES, T. N. Effects of nicotine on heart rate studied by direct perfusion of sinus node. *American Journal of Physiology* 212(4) : 911-916, April 1967.
- (143) OSKI, F. A., GOTTLIEB, A. J., MILLER, W. W., DELIVORIA-PAPADOPOULOS, M. The effects of deoxygenation of adult and fetal hemoglobin on the synthesis of red cell 2,3-diphosphoglycerate and its *in vivo* consequences. *Journal of Clinical Investigation* 49(2) : 400-407, February 1970.
- (144) PAFFENBARGER, R. S., JR., LAUGHLIN, M. E., GIMA, A. S., BLACK, R. A. Work activity of longshoremen as related to death from coronary heart disease and stroke. *New England Journal of Medicine* 282(20) : 1109-1114, May 14, 1970.

- (145) PAPPENBARGER, R. S., JR., WILLIAMS, J. L. Chronic disease in former college students. V. Early precursors of fatal stroke. *American Journal of Public Health and the Nation's Health* 57(8): 1290-1299, August 1967.
- (146) PAPPENBARGER, R. S., JR., WING, A. L. Chronic disease in former college students. X. The effects of single and multiple characteristics on risk of fatal coronary heart disease. *American Journal of Epidemiology* 90(6): 527-535, December 1969.
- (147) PAGE, I. H., LEWIS, L. A., MOINUDDIN, M. Effect of cigarette smoking on serum cholesterol and lipoprotein concentrations. *Journal of the American Medical Association* 171(11): 1500-1502, November 14, 1959.
- (148) PAUL, O., LEPPER, M. H., PHELAN, W. H., DUPERTUIS, G. W., MACMILLAN, A., MCKEAN, H., PARK, H. A longitudinal study of coronary heart disease. *Circulation* 28(1): 20-31, July 1963.
- (149) PENTECOST, B., SHILLINGFORD, J. The acute effects of smoking on myocardial performance in patients with coronary arterial disease. *British Heart Journal* 26: 422-429, 1964.
- (150) PINCHERLE, G., WRIGHT, H. B. Screening in the early diagnosis and prevention of cardiovascular disease. *Journal of the College of General Practitioners* 13: 280-289, 1967.
- (151) POZNER, H., BILLIMORIA, J. D. Effect of smoking on blood-clotting and lipid and lipoprotein levels. *Lancet* 1(7660): 1318-1321, June 20, 1970.
- (152) PURI, P. S., ALAMY, D., BING, R. J. Effect of nicotine on contractility of the intact heart. *Journal of Clinical Pharmacology* 8(5): 295-301, September-October 1968.
- (153) RAZDAN, A. N., SINGH, R. P., SRIVASTAVA, V. K. Thromboangiitis obliterans. A clinical study of 125 cases. *International Surgery; Bulletin* 47(2): 122-125, February 1967.
- (154) REGAN, T. J., HELLEMS, H. K., BING, R. J. Effect of cigarette smoking on coronary circulation and cardiac work in patients with arteriosclerotic coronary disease. *Annals of the New York Academy of Sciences* 90(1): 186-189, September 27, 1960.
- (155) REID, D. D., HOLLAND, W. W., ROSE, G. A. An Anglo-American cardiovascular comparison. *Lancet* 2(7531): 1375-1378, December 30, 1967.
- (156) ROMERO, T., TALESNIK, J. Influence of nicotine on the coronary circulation of the isolated heart of the cat. *Journal of Pharmacy and Pharmacology* 19(5): 322-328, 1967.
- (157) ROSE, G. A. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bulletin of the World Health Organization* 27(6): 645-658, 1962.
- (158) ROSE, G. A. Chest pain questionnaire. *Milbank Memorial Fund Quarterly* 43(2, part 2): 32-39, April 1965.
- (159) ROSENMAN, R. H., FRIEDMAN, M., STRAUS, R., WURM, M., KOSITCHEK, R., HAHN, W., WERTHESEN, N. T. A predictive study of coronary heart disease. The Western Collaborative Group Study. *Journal of the American Medical Association* 189(1): 15-22, July 6, 1964.
- (160) ROSS, G., BLESIA, M. I. The effect of nicotine on the coronary circulation of dogs. *American Heart Journal* 79(1): 96-102, January 1970.
- (161) ROTH, G. M., SCHICK, R. M. The effects of smoking on the peripheral circulation. *Diseases of the Chest* 37(2): 203-210, February 1960.

- (162) ROTTENSTEIN, H., PEIRCE, G., RUSS, E., FELDER, D., MONTGOMERY, H. Influence of nicotine on the blood flow of resting skeletal muscle and of the digits in normal subjects. *Annals of the New York Academy of Sciences* 90(1) : 102-113, September 27, 1960.
- (163) RUSSEK, H. I., ZOHMAN, B. L. Relative significance of heredity, diet and occupational stress in coronary heart disease of young adults. Based on an analysis of 100 patients between the ages of 25 and 40 years and a similar group of 100 normal control subjects. *American Journal of the Medical Sciences* 235(3) : 266-277, March 1958.
- (164) RUSSEK, H. I., ZOHMAN, B. L., DORSET, V. J. Effects of tobacco and whiskey on the cardiovascular system. *Journal of the American Medical Association* 157(7) : 563-568, February 12, 1955.
- (165) SACKETT, D. L., GIBSON, R. W., BROSS, I. D. J., PICKREN, J. W. Relation between aortic atherosclerosis and the use of cigarette and alcohol. An autopsy study. *New England Journal of Medicine* 279(26) : 1413-1420, December 26, 1968.
- (166) SAPHIR, R., RAPAPORT, E. Cardiovascular responses of the cat to mesenteric intra-arterial administration of nicotine, cyanide and venous blood. *Circulation Research* 25(6) : 713-724, December 1969.
- (167) SCHIMMLER, W., NEFF, C., SCHIMERT, G. Risikofaktoren und Herzinfarkt. Eine retrospektive studie. (Risk factors and myocardial infarct. A retrospective study.) *Münchener Medizinische Wochenschrift* 110(27) : 1585-1594, July 5, 1968.
- (168) SCHWARTZ, D., LELLOUCH, J., ANGUERA, G., RICHARD, J. L., BEAUMONT, J. L. Etiologie comparee de l'arteriopathie oblitterante des membres inferieurs et de l'arteriopathie coronarienne. (Comparative etiology of lower limb obliterative arteriopathy and of coronary arteriopathy.) *Archives des Maladies du Coeur* 58: Supplement No. 3, 24-32, 1965.
- (169) SCHWARTZ, D., LELLOUCH, J., ANGUERA, G., BEAUMONT, J. L., LENEGRE, J. Tobacco and other factors in the etiology of ischemic heart disease in man: Results of a retrospective survey. *Journal of Chronic Diseases* 19(1) : 35-55, January 1966.
- (170) SELTZER, C. C. The effect of cigarette smoking on coronary heart disease. Where do we stand now? *Archives of Environmental Health* 20(3) : 418-423, March 1970.
- (171) SEN GUPTA, A. N., GHOSH, B. P. Observations on some cardiovascular and biochemical effects of tobacco smoking in health and in ischaemic cardiaes. *Bulletin of the Institute of Post-Graduate Medical Education and Research* 9(2) : 45-57, April 1967.
- (172) SHAPIRO, S., WEINBLATT, E., FRANK, C. W., SAGER, R. V. Incidence of Coronary Heart Disease in a Population Insured for Medical Care (HIP). Myocardial infarction, angina pectoris, and possible myocardial infarction. *American Journal of Public Health and the Nation's Health* 59(6) : Supplement to June 1969. 101 pp.
- (173) SHEPHERD, J. T. Effect of cigarette-smoking on blood flow through the hand. *British Medical Journal* 2: 1007-1010, October 27, 1951.
- (174) SOGANI, R. K., JOSHI, K. C. Effect of cigarette and biri smoking and tobacco chewing on blood coagulation and fibrinolytic activity. *Indian Heart Journal* 17: 238-242, July 1965.
- (175) SPAIN, D. M., BRADESS, V. A. Sudden death from coronary heart disease. Survival time, frequency of thrombi, and cigarette smoking. *Chest* 58(2) : 107-110, August 1970.

- (176) SPAIN, D. M., NATHAN, D. J. Smoking habits and coronary atherosclerotic heart disease. *Journal of the American Medical Association* 177 (10) : 683-688, September 9, 1961.
- (177) STAMLER, J., BERKSON, D. M., LEVINSON, M., LINDBERG, H. A., MOJONNIER, L., MILLER, W. A., HALL, Y., ANDELMAN, S. L. Coronary artery disease. Status of preventive efforts. *Archives of Environmental Health* 13(3) : 322-335, September 1966.
- (178) STEFANOVICH, V., GORE, I., KAJIYAMA, G., IWANAGA, Y. The effect of nicotine on dietary atherogenesis in rabbits. *Experimental and Molecular Pathology* 11(1) : 71-81, August 1969.
- (179) STEJFA, M., JR. Predictive significance of risk factors in exertional angina pectoris. *Cardiologia* 51(6) : 336-339, 1967.
- (180) STROBEL, M., GSELL, O. Mortalität in Beziehung zum Tabakrauchen: 9 Jahre Beobachtungen bei Ärzten in der Schweiz. (Mortality in relation to tobacco smoking. Nine years of observation in Swiss doctors.) *Helvetica Medica Acta* 32(6) : 547-592, December 1965.
- (181) STROMBLAD, B. C. R. Effect of intra-arterially administered nicotine on the blood flow in the hand. *British Medical Journal* 1: 484-485, February 21, 1959.
- (182) STRONG, J. P., RICHARDS, M. L., MCGILL, H. C., JR., EGGEN, D. A., MCMURRAY, M. T. On the association of cigarette smoking with coronary and aortic atherosclerosis. *Journal of Atherosclerosis Research* 10(3) : 303-317, November-December 1969.
- (183) TAYLOR, H. L., BLACKBURN, H., KEYS, A., PARLIN, R. W., VASQUEZ, C., PUCHNER, T. Five-year follow-up of employees of selected U.S. railroad companies. IN: Keys, A. (Editor). *Coronary Heart Disease in Seven Countries*. American Heart Association Monograph No. 29, 1970. pp. 20-39.
- (184) THIENES, C. H. Chronic nicotine poisoning. *Annals of the New York Academy of Sciences* 90(1) : 239-248, September 27, 1960.
- (185) THOMAS, C. B. Familial and epidemiologic aspects of coronary disease and hypertension. *Journal of Chronic Diseases* 7(3) : 198-208, March 1958.
- (186) THOMAS, C. B., MURPHY, E. A. Circulatory responses to smoking in healthy young men. *Annals of the New York Academy of Sciences* 90(1) : 266-276, September 27, 1960.
- (187) TIBBLIN, G. High blood pressure in men aged 50. A population study of men born in 1913. *Acta Medica Scandinavica (Supplementum 470)* : 1-84, 1967.
- (188) TIBBLIN, G. Kommentar till en svensk tvillingundersökning. (Comment on research on twins in Sweden.) *Lakartidningen* 65 (47) : 4654-4655, November 20, 1968.
- (189) TRAVELL, J., RINZLER, S. H., KARP, D. Cardiac effects of nicotine in the rabbit with experimental coronary atherosclerosis. *Annals of the New York Academy of Sciences* 90(1) : 290-301, September 27, 1960.
- (190) TRUETT, J., CORNFIELD, J., KANNEL, W. A multivariate analysis of the risk of coronary heart disease in Framingham. *Journal of Chronic Diseases* 20: 511-524, 1967.
- (191) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking*. A Public Health Service Review: 1967. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1967. 199 pp.

- (192) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. 1968 Supplement to the 1967 Public Health Service Review. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1968. 117 pp.
- (193) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. 1969 Supplement to the 1967 Public Health Service Review. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696-2, 1969. 98 pp.
- (194) U.S. PUBLIC HEALTH SERVICE. NATIONAL AIR POLLUTION CONTROL ADMINISTRATION. Air Quality Criteria for Carbon Monoxide. Washington, U.S. Department of Health, Education and Welfare, National Air Pollution Control Administration Publication No. AP-62, March 1970. 158 pp.
- (195) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Vital and Health Statistics. Data from the National Health Survey. Coronary Heart Disease in Adults—United States—1960-1962. Washington, U.S. Department of Health, Education and Welfare, National Center for Health Statistics Series 11, No. 10, September 1965. 46 pp.
- (196) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Vital Statistics of the United States—1967, Vol. II.—Mortality, Part A. Washington, U.S. Department of Health, Education and Welfare, Public Health Service Publication, 1969.
- (197) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Vital Statistics Rates in the United States 1940-1960. Washington, U.S. Department of Health, Education and Welfare, Public Health Service Publication No. 1677, 1968. 881 pp.
- (198) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.
- (199) VAN BUCHEM, F. S. P. Serum lipids, nutrition and atherosclerotic complications in man. *Acta Medica Scandinavica* 181(4) : 403-416, April 1967.
- (200) VIEL, B., DONOSO, S., SALCEDO, D. Coronary atherosclerosis in persons dying violently. *Archives of Internal Medicine* 122(2) : 97-103, August 1968.
- (201) VILIGER, U., HEYDEN-STUCKY, S. Das Infarktprofil. Unterschiede zwischen infarktpatienten und Kontrollpersonen in der Ostschweiz. (The infarct profile. Differences between infarct patients and controls in East Switzerland.) *Schweizerische Medizinische Wochenschrift* 96(23) : 748-758, June 11, 1966.
- (202) VON AHN, B. Tobacco smoking, the electrocardiogram, and angina pectoris. *Annals of the New York Academy of Sciences* 90(1) : 190-198, September 27, 1960.
- (203) WATTS, D. T. The effect of nicotine and smoking on the secretion of epinephrine. *Annals of the New York Academy of Sciences* 90(1) : 74-80, September 27, 1960.
- (204) WEBSTER, W. S., CLARKSON, T. B., LOFLAND, H. B. Carbon monoxide-aggravated atherosclerosis in the squirrel monkey. *Experimental and Molecular Pathology* 13(1) : 36-50, 1970.
- (205) WEIR, J. M., DUNN, J. E., JR. Smoking and mortality: A prospective study. *Cancer* 25(1) : 105-112, January 1970.

- (206) WENZEL, D. G., BECKLOFF, G. L. The effect of nicotine on experimental hypercholesterolemia in the rabbit. *Journal of the American Pharmaceutical Association; Scientific Edition* 47(5) : 338-343, May 1958.
- (207) WENZEL, D. G., TURNER, J. A., KISSIL, D. Effect of nicotine on cholesterol-induced atherosclerosis in the rabbit. *Circulation Research* 7: 256-261, March 1959.
- (208) WEST, J. W., GUZMAN, S. V., BELLET, S. Cardiac effects of intracoronary arterial injections of nicotine. *Circulation Research* 6: 389-395, May 1958.
- (209) WESTFALL, T. C., CIPOLLONI, P. B., EDMUNDOWICZ, A. C. Influence of propranolol on hemodynamic changes and plasma catecholamine levels following cigarette smoking and nicotine. *Proceedings of the Society for Experimental Biology and Medicine* 123: 174-179, 1966.
- (210) WESTFALL, T. C., WATTS, D. T. Effect of cigarette smoke on epinephrine secretion in the dog. *Proceedings of the Society for Experimental Biology and Medicine* 112(4) : 843-847, April 1963.
- (211) WESTFALL, T. C., WATTS, D. T. Catecholamine excretion in smokers and nonsmokers. *Journal of Applied Physiology* 19(1) : 40-42, January 1964.
- (212) WHEREAT, A. F. Is atherosclerosis a disorder of intramitochondrial respiration? *Annals of Internal Medicine* 73(1) : 125-127, July 1970.
- (213) WIDMER, L. K., HARTMANN, G., DUCHOSAL, F., PLECHL, S.-C. Risk factors in arterial occlusion of the limbs. *German Medical Monthly* 14(10) : 476-479, October 1969.
- (214) WILENS, S. L., PLAIR, C. M. Cigarette smoking and arteriosclerosis. *Science* 138: 975-977, November 30, 1962.
- (215) WYNDER, E. L., HOFFMANN, D. *Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis*. New York, Academic Press, 1967. 730 pp.

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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.	<i>Percent Smokers</i>				<i>Percent Smokers</i>					
			<i>Age</i>									
			40-49	50-59	60-69	70 or over	40-49	50-59	60-69	70 or over		
			79.7 (187)	71.7 (382)	63.8 (431)	69.8	61.9 (302)	73.9 (371)	61.8 (327)	66.3	(p<0.001) (not significant) (not significant) (p<0.05)	
Mills and Porter, 1957, U.S.A. (131).	474 white male coronary deaths. Controls: 606 white males.	Undefined.										
				40-49	50-59	60-69	70 or over	40-49	50-59	60-69		70 or over
				(56)	(135)	(153)	(130)	(216)	(188)	(114)		(88)
			NS	7.14	6.66	18.30	33.84	19.91	24.47	35.09		54.12
			All cigarettes	83.93	82.23	49.02	18.44	70.83	59.94	43.86	16.47	
			Pipes, cigars	8.93	11.11	32.68	47.70	9.26	16.47	21.05	29.41	
Buechley et al., 1958, U.S.A. (33).	Males reporting CHD to California Health Survey with matched controls from same survey (included those surviving first myocardial infarction).	Questionnaire and interview.	NS	20.4	(23)					NS	42.1	(51)
			≤20	61.1	(69)					≤20	46.3	(56)
			>20	18.5	(21)					>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.	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.	<i>Tobacco usage > 50 cigarettes/day</i> 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 (185, 186)	400 males less than 60 years of age with classical CHD. Data compared with male population consumption figures.	Interview.	<i>Males</i> NS 4.50 (18) SM 90.75 (363) EX 4.75 (19) Total 100.00 (400)	<i>Males</i> 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.

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)		Controls (percent)		Comments	
			Males (72)	Females (28)	Males (72)	Females (28)		
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.	NS	6.94	71.4	†25.0	82.1	These are not pure smoking classes. †(p<0.01)
			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) (only 28 were mixed or cigar smokers)		100.0 (413) (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)	21.0 (33)	
			1-9 cigarettes per day 7.0 (5)	10.5 (13)	
			10-15 25.4 (18)	33.9 (42)	
			16-20 35.2 (25)	25.8 (32)	
			21-34 22.5 (16)	17.7 (22)	
			>35 9.9 (7)	12.1 (15)	
			All SM 100.0 (71)	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)	45.6 (261)	Smoking on controls obtained from statistics of smoking in Irish Republic. Sudden death not included.
			NS 33.0 (33)	45.3 (259)	
			EX 4.0 (4)	9.1 (52)	
			Total 100.0 (100)	100.0 (572)	
Stejfa, 1967, Poland (179).	70 male and female patients with recent onset exertional angina pectoris. 54 controls of same age.	Direct interviews.	<i>Prevalence of risk factors</i>		Authors then followed the 70 patients for 3 years and noted that smoking significantly influenced the incidence of coronary occlusion.
			<i>Angina patients</i> 60.0	<i>Control group</i> 48.1 (p>0.1)	
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)	26.0 (187) (p<0.001)	
			EX 12.0 (59)	20.0 (142) (p<0.001)	
			Cigar, pipe 12.0 (62)	11.0 (77)	
			<19 cigarettes 25.0 (129)	14.0 (101) (p<0.001)	
			>20 42.0 (209)	29.0 (207) (p<0.001)	
			Total 100.0 (503)	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 smoked1.75	24.2	
			EX before infarction1.75	19.7	
			EX after infarction29.1	..	
			<15 cigarettes28.3	27.4	
			>15 cigarettes22.6	20.0	
			All80.0	47.4	
Pipe16.5	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.	NS20.0 (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.	<i>Difference between SM and NS</i>				
			<i>Ages 20-29</i>	<i>Ages 30-39</i>	<i>Ages 40-59</i>	
		Lipid:	(NS 55, SM 37)	(NS 56, SM 67)	(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		
Thomas, 1958, U.S.A. (185).	521 medical students.	<i>Serum cholesterol mg. percent</i>				
			NS (264)	SM (257)		
			<i>Observed/Expected</i>	<i>Observed/Expected</i>		
		<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.	<i>Serum cholesterol mg. percent</i>			The authors conclude that there is evidence of a gradient of cholesterol with increasing amount of cigarette smoking in younger men.	
			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)			
Karvonen et al., 1959, Finland (97).	525 males in various occupations 20-59 years of age.	<i>Serum cholesterol mg. percent</i>			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.	
			<i>West Finland</i>	<i>East Finland</i>		<i>Helsinki</i>
		NS	208.0 (64)	226.6 (39)		235.1 (62)
		SM	228.7 (91)	249.7 (103)		257.8 (166)

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.	<i>Mean serum cholesterol mg. percent</i> Mean Beta/Alpha lipoprotein ratio							
	NS	214 (38)	2.0 (36)						
	5 cigarettes/day	201 (12)	2.1 (11)						
	10	213 (34)	1.9 (33)						
	20	201 (33)	1.9 (35)						
	>30	206 (8)	1.8 (8)						
Bronte-Stewart, 1961, South Africa (31).	Approximately 600 healthy males 25-55 years of age.	<i>Cholesterol mg. percent</i> 25-39 40-55 †A ‡E A E		No data given on numbers in each group. †A—African. ‡E—European.					
	NS	179	197		222	246	2.89	3.34	3.75
	"Heavy" SM	186	223	204	236	3.82	4.40	4.07	5.40
Konttinen, 1962, Finland (119).	314 male military recruits 18-25 years of age.	<i>Serum cholesterol mg. percent</i> NS (145)		No serum lipid differences found among the various smoking groups.					
	(Cigarettes per day) 1-10	(53)	206.8		218.0				
	11-19	(54)	213.1		222.3				
	>20	(62)	202.3		224.7				
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.	<i>Serum cholesterol mg. percent</i>				No statistically significant differences found between SM and NS.	
			<i>Ages <39</i>	<i>40-49</i>	<i>50-59</i>		<i>60-69</i>
		NS	195 (12)	189 (10)		176 (7)
		<20 cigarettes/day	208 (5)	201 (16)	202 (13)		195 (10)
		>20 cigarettes/day	197 (5)	175 (7)	171 (7)		..
		<i>Serum triglycerides mg. percent</i>					
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	..			
Kedra and Dmowski, 1966, Poland (99).	200 clinically healthy males 20-50 years of age.	<i>Serum cholesterol mg. percent</i>		<i>Phospholipids mg. percent</i>		Serum cholesterol also noted to increase with increasing intensity and duration of smoking.	
		NS(100)	170.2	} p<0.01	268.1		} p>0.05
		SM 100)	224.9		257.5		
		<i>Total fatty acids mg. percent</i>		<i>Beta-lipoproteins percent of total lipoproteins</i>			} p<0.01
		NS(100)	797.8	43.1			
		SM 100)	869.9	49.9			
Harlan et al., 1967, U.S.A. (79).	657 former naval aviation cadets 48 years of age (average).	<i>Serum cholesterol</i>		<i>Serum triglycerides</i>		<i>Lipoproteins</i>	
		Found to be related to cigarette smoking p<0.05.		Found not to be related to cigarette smoking.		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.	<i>Serum cholesterol mg. percent</i>		<i>Serum triglycerides mg. percent</i>		No statistically significant difference found between SM and NS.	
		<10 cigarettes/day	210.0 (334)	110.0			
		>10 cigarettes/day	260.0 (166)	180.0			

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.	NS	<i>Males</i>		<i>Females</i>			
			Cigarette	209.9 (360)	210.1 (1,439)		212.5 (1,426)	212.4 (910)
Pincherly and Wright, 1967, England (159).	2,000 men participating in executive health examinations 28-70 years of age.	NS (677)	<i>Serum cholesterol mg. percent</i>		<i>Percentage with serum cholesterol >270 mg. percent</i>	The authors noted that smokers showed significantly higher (p<0.001) serum cholesterol levels than nonsmokers.		
			Ex-smoker (388)	236.2	246.0		19.0	28.0
			1-19 cigarettes/day (424)	239.2	249.4		24.0	30.0
			>20 cigarettes/day (511)	249.4	249.4		30.0	30.0
Van Buchem, 1967, Netherlands (199).	918 randomly chosen males 40-59 years of age for entry into prospective study.	NS	<i>Serum cholesterol</i>			The authors found no correlation between smoking and serum cholesterol levels.		
				<i>0-209 mg. percent</i>	<i>210-249 mg. percent</i>		<i>>250 mg. percent</i>	
			Cigarette SM	12.4 (32)	14.0 (44)		14.2 (41)	
			Other	71.6 (184)	67.8 (213)		68.2 (197)	
Boyle et al., 1968, U.S.A. (28).	1,104 male factory employees 20-64 years of age.	NS	<i>Serum cholesterol mg. percent</i>		<i>Serum Beta-lipoprotein mg. percent</i>	Beta-lipoproteins were found to increase with age, but smokers had higher levels than nonsmokers at all ages.		
			SM	243 (519)	251 (576)		0.325	0.351
Caganova et al., 1968, Czechoslovakia (36).	49 males living in youth hostel, 21.6 average age.	NS (34)	<i>Serum cholesterol mg. percent</i>		<i>Serum Beta-lipoprotein mg. percent</i>			
			SM (15)	188.20	214.20		359.80	498.40
				p<0.025			p<0.001	
				<i>Beta/alpha lipoprotein ratio</i>			p<0.025	
		NS (34)	1.16	1.55				
		SM (15)	1.55					

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 (139).	140 males 20-68 years of age.	<i>Serum-cholesterol</i> NS (20) p<0.01 Heavy smokers	<i>Serum Beta-lipoproteins</i> NS p<0.01 Heavy smokers	<i>Serum free fatty acids</i> NS p<0.01 Heavy smokers	
Kjeldsen, 1969, Denmark (113).	934 employees of various firms in Copenhagen.	<i>Serum cholesterol mg. percent</i>			
		NS (196)	236	} p<0.01	
		SM (738)	247		
Pozner and Billimoria, 1970, England (151).	64 male and female healthy volunteers 19-30 years of age.	<i>Serum cholesterol mg. percent</i>			Significant figures refer to heavy smokers as compared with nonsmokers.
		NS (20)	176.3	<i>Serum triglycerides mg. percent</i> 68.6	
		Light SM (17) (Over 7.3 cigarettes/day)	172.1	68.4	
		Heavy SM (27) (Over 22.5 cigarettes/day)	200.0 p<0.05	87.6 p>0.05	
				<i>Total phospholipids mg. percent</i> 193.4	
				188.9	
				215.0 p<0.001	

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

TABLE A8.—*Blood pressure differences between smokers and nonsmokers*(Actual number of individuals shown in parentheses)¹

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments			
Dawber et al., 1959, U.S.A. (47).	1,253 male and female residents of Framingham.	<i>Systolic blood pressure</i>		No association found between systolic blood pressure and smoking.		
		<i>Ages 29-44</i>				
		NS (149)	138.8		45-59	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.	<i>Proportion of males with "Hypertension" ($\geq 200/\geq 100$ mm. Hg.)</i>				
		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.	<i>Systolic blood pressure</i>			No data on pipe and cigar smokers. No statistical significance noted.	
			<i>West Finland</i>	<i>East Finland</i>		<i>Helsinki</i>
		NS	139.2 (64)	142.6 (39)		132.8 (62)
		SM	133.2 (91)	135.4 (103)		129.8 (166)
			<i>Diastolic blood pressure</i>			
		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.	<i>Mean systolic blood-pressure</i>		Nonsmoker and smoker groups were of similar average age.
NS (728)	137.0			} ($p \leq 0.05$)		
SM (407)	133.6					
	<i>Mean diastolic blood-pressure</i>					
		83.9	} ($p \leq 0.05$)			
		82.5				

TABLE A8.—Blood pressure differences between smokers and nonsmokers (cont.)
 (Actual number of individuals shown in parentheses)¹
 [SM = Smokers NS = Nonsmokers]

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

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					Total
		Former cigarette smokers	Current and former pipe and cigar only	Cigarettes			
				1-15	16-25	26 and over	
A	15.3 (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	Never smoked	Smoking group					Total
		Former cigarette smokers	Current and former pipe and cigar only	Cigarettes			
				1-15	16-25	26 and over	
A	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. Nicotine intravenous 0.2-1.2 mg./kg.	Definite increase. Definite increase.	Definite increase. Definite increase.			Coronary artery ligation increased the frequency of nicotine-induced severe arrhythmias; these became less evident with increasing time since ligation.
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 μ g./kg. II. 0.04-1 μ g./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 $\mu\text{g./kg./minute}$.		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 $\mu\text{g./kg.}$ intravenously. Epinephrine 5 $\mu\text{g./kg.}$ 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. (139).	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, country, reference	Number and type of population	Smoking procedure	Comments	
Bellet et al., 1962, U.S.A. (22).	I. 10 normal dogs	Intravenous nicotine,	I. 125 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.
	II. 9 dogs at varying intervals following coronary artery ligation.	20 $\mu\text{g.}/\text{kg.}/\text{minute}$ for 15-20 minutes.	II. 82.5 percent increase	
	III. 7 dogs with varying grades of artificially-induced coronary artery narrowing.		III. 83.3 percent increase	
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 $\text{mg.}/\text{kg.}/\text{minute}$ 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 $\mu\text{g./kg.}$ intravenous nicotine, (b) 40 $\mu\text{g./kg.}$ intravenous nicotine. II. Experimental (3), 4 $\mu\text{g./kg.}$ 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 $\mu\text{g./cc.}$ 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 $\mu\text{g./kg.}$ 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. intra-coronary 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).	1 standard and 1 denicotinized cigarette.	I. 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.
	II. 37 male patients with overt clinical CHD 42-70 years of age (average 54), 6 were nonsmokers.		II. Increase.	Increase.					
Bargeron et al., 1957, U.S.A. (17).	14 of 30 healthy adult male volunteer smokers and nonsmokers who underwent successful catheterization 18-53 years of age.	1 cigarette inhaled at intervals of 20 seconds.	Insignificant increase.	Increase.				Definite increase.	Coronary vascular resistance fell significantly. Myocardial O ₂ usage underwent no significant change. Pyruvate extraction fell slightly. Authors consider lack of increase in heart rate as due to baseline apprehensive tachycardia.

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

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Regan et al., 1960, U.S.A. (154).	7 males with history of EKG-proven myocardial infarction undergoing cardiac catheterization.	2 standard cigarettes in 25 minutes inhaled at minute intervals.	Definite increase.	Definite increase.			Increase.	No significant change.	Myocardial O_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 non-smokers. 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. (b) Non-inhalation smoking. (c) 2 standard cigarettes in 10 minutes. (d) Nicotine 0.6 mg. intravenously.	(a) No change. (b) No change. (c) Definite increase. (d) Definite increase.	No change. No change. Widened pulse, pressure. Definite increase.		(a) No change. (b) No change. (c) Definite increase. (d) Definite increase.	No change. No change. Definite increase. Definite change.		Cardiac output measured by dye dilution technique.

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
Pontecost and Shillingford, 1964, U.S.A. (179)	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. (67)	5 male and 3 female patients with healed myocardial infarction 48-69 years of age 2/8 non-smokers.	2 standard cigarettes in 10 minutes at rest and under graded exercise.	Definite increase at rest and at exercise.			No significant changes at rest or during exercise.	No significant changes at rest or during exercise.		The author contrasts this response with that seen among healthy young individuals.

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. (205).	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).	Mongrel 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 to 2.5 cc. of 3 percent solution for 1 month.	I. 4/6 animals died of infection and showed marked edema and focal hyalinization of the media of the aorta and large elastic arteries. 2/6 animals were sacrificed and showed thickening and hyalinization of the walls of the coronary arteries and edema of the media as well as endothelial proliferation of other arteries.
	II. 60 rats.	Increasing doses up to 1 cc. of 1 percent solution for 1 month.	II. Much less aortic involvement than that found in the dogs; infrequent arteriolar changes consisting of fibrosis and thickening of the media.
Maslova, 1956, USSR (130).	Rabbits	I. (10) Nicotine subcutaneously 1 percent solution 0.2 cc. daily for 115 days.	I. Aortic wall--acute swelling of elastic fibers with focal fragmentation and partial disintegration--no intimal fat deposits seen. Coronary vessels--thickening of the vessel wall--no fat deposits.
		II. (14) Nicotine plus 0.2 grams cholesterol per day.	II. Aorta--"massive" deposits of "cholesterol" in the intima and vasa vasorum with "loosening" of the aortic wall. Coronary vessels--the larger vessels showed moderate fat deposition and the smaller vessels showed swelling of the elastica.
		III. (10) Cholesterol only.	III. Aorta--isolated lipid deposition in the arch and ascending portions only. Coronary vessels--no fat deposition.
Czochra-Lysanowicz et al., 1959, U.S.A. (46).	Rabbits	I. (10) 1.0 g. cholesterol/day for 100 days.	Index of aortic lesion density (cholesterol infiltration): I. 2.5.
		II. (10) Cholesterol plus 0.0015 g. nicotine/day intravenously.	II. 3.4.
		III. (4) Nicotine only.	III. No aortic lesions noted.

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

Author, year, country, reference	Number and type of animal	Procedure	Results
Wenzel et al., 1959, U.S.A. (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.
Grosogeat 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	<i>Nicotine</i>	<i>Diet</i>	<i>Vitamin D</i>	
		I. (8) Control	Control	Control	I. Infrequent medial calcific disease without lipid localization.
		II. (7) Control	Cholesterol	Control	II. No medial calcific disease but frequent intimal atheroma formation.
		III. (14) Nicotine	Control	Control	III. Rare calcific medial degeneration; no intimal atheromatous disease.
		IV. (15) Nicotine	Cholesterol	Control	IV. The largest number of atheromatous lesions.
		V. (9) Control	Cholesterol	Vitamin D	V. No medial calcific disease.
		VI. (14) Nicotine	Cholesterol	Vitamin D	VI. Consistent medial calcific disease.
		(Sacrificed at various times)			
		Control—no treatment.			
		Nicotine—subcutaneous injections in oil—increasing amounts 2 times per week.			
		Vitamin D—subcutaneous injections up to $6-8 \times 10^5$ IU.			
		Cholesterol—250-500 mg. cholesterol added per 100 g. diet.			
Choi, 1967, Korea (42).	Albino rabbits	I. Nicotine 1-5 mg./kg./day intraperitoneally.			I. Increasing nicotine dosages were associated with decreased atheroma formation (findings not statistically significant).
		Cholesterol 1 g./day (in varying combinations with controls).			
		II. Nicotine alone.			II. Nicotine alone produced no atheroma formation but was associated with the presence of aortic medial calcification and endothelial hyperplasia.
		III. Cholesterol alone. (Sacrificed at 60 days)			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		<i>Percent of aortic surface involved with atherosclerosis</i>	In both stock and cholesterol-fed animals, nicotine was also noted to increase aortic triglyceride content and to decrease aortic free cholesterol content.
		2.78 mg./kg./day, 5/7 days.			
		II. (10) Cholesterol only.		I. 9.4	
		III. (10) Nicotine only.		II. 5.7	
		IV. (10) Control.		III. 0.1	
				IV. . .	

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.			<i>Serum lipoproteins</i> 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.	<i>Mean rise</i> I. 351 μ Eq./L. II. 9.8 μ Eq./L. III. 272-2,304 μ Eq./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.	<i>Mean rise</i> I. 858 μ Eq./L. II. 320 μ Eq./L. III. 292 μ Eq./L. IV. 20 μ Eq./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 camphor-sulfonate (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.
Kontinen 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 with a leveling of response at 4 weeks. Group IV showed a further increase at 8-12 week period.	The authors consider an elevated cholesterol/ phospholipid ratio to be a notable indication of atherogenic susceptibility. The concomitant increase in phospholipids with the cholesterol may negate the importance of nicotine-induced hypercholesterolemia as an atherogenic stimulus.
Kershbaum et al., 1961, U.S.A. (194).	5 mongrel dogs.	Intravenous infusion of 20 mg./kg. nicotine in 20 minutes.	Definite increase in 13/15 observations.				
Kershbaum et al., 1965, U.S.A. (107).	20 adult mongrel dogs.	I. 9 received IM nicotine daily for 6 weeks; up to 1 mg./kg. II. 5 placebo injection. III. 6 control.	I. Significant increase in 8/9 dogs. II. No change. III. No change.		No change in any group.		

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

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

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

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

TABLE A27.—*Smoking and thrombosis*

Author, year, country, reference	Number and type of population	Experimental conditions ¹	Whole blood clotting time	Pro-thrombin time	Partial thromboplastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Blackburn et al., 1959, U.S.A. (25).	16 adult schizophrenic patients, 8 university students, all smokers.	12 individuals smoked 2 high-nicotine standard brand cigarettes.									Plasma stypven time (-)	
Mustard and Murphy, 1963, U.S.A. (141).	7 white males with either CVD or COPD, all heavy smokers 35-72 years of age.	Compared after periods of abstinence or continuation of smoking.	(-)	(-)	(-)		(-)	(-)	(+) decrease	(+) increase	Platelet clumping time (±)	
Ambrus and Mink, 1964, U.S.A. (4).	20 healthy non-smoking medical students <30 years of age.	Deep inhalation of one nonfiltered cigarette.	(-)		(-)	(-)	(±) increase	(-)			Thromboplastin 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	Pro-thrombin time	Partial thromboplastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Sogani and Joshi, 1965, India (174).	11 observations on male smokers all regular tobacco users.	Smoked 2 cigarettes or 2 biris or chewed 1 betel nut quid in 20 minutes.	(-)	(-)		(-)	(+) increase				Fibrinolysis (+) decrease	Bir-- tobacco wrapped in tobacco leaf.
Engelberg, 1965, U.S.A. (58).	40 male and 20 female hospital patients, all smokers 17-68 years of age.	2 cigarettes in 20 minutes.									Chandler (in vitro) thrombosis time + decrease	
Kedra and Korolko, 1965, Poland (100).	39 male and 11 female smokers and 24 male and 26 female nonsmokers 18-25 years of age.	5 cigarettes in 1 hour.	(±) decrease	(-)		(+) decrease					Thrombin time (±) decrease	
Murchison and Fyfe, 1966, Scotland (139).	8 males and 4 female patients with various diseases, all heavy smokers 37-67 years of age.	2 cigarettes in 15 minutes, lit or unlit cigarettes.					(+) (+) increase					† Smoking both lit and unlit cigarettes caused a rise in platelet adhesiveness which the authors correlated with rise in plasma non-esterified fatty acids.

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

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

Symbols:

— — No effect.

+ . . . Questionable effect.

+ = Definite effect.

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

CHAPTER 3

Chronic Obstructive Bronchopulmonary Disease

Contents

	<i>Page</i>
Introduction.....	139
Epidemiological Studies.....	141
COPD Mortality.....	141
COPD Morbidity.....	145
Ventilatory Function.....	146
Genetic Factors.....	148
Alpha ₁ -antitrypsin.....	150
Air Pollution.....	152
Occupational Hazards.....	153
Cadmium.....	154
Pathological Studies.....	154
Experimental Studies.....	158
Animal Studies.....	158
Studies in Humans.....	163
Studies Concerning Pulmonary Clearance.....	164
Overall Clearance.....	164
Ciliary Function.....	164
Phagocytosis.....	165
Studies Concerning the Surfactant System.....	172
Other Respiratory Disorders.....	172
Infectious Respiratory Diseases.....	172
Postoperative Complications.....	174
Summary and Conclusions.....	175
References.....	176

FIGURES

1. Percent of lung sections with Grade IV or V fibrosis . . .	161
2. Percent of lung sections with Grade II or III emphysema	162

LIST OF TABLES

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

1. Chronic obstructive bronchopulmonary disease mortality ratios.....	142
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LIST OF TABLES (Continued)

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

	<i>Page</i>
A2. Smoking and chronic obstructive pulmonary disease symptoms—percent prevalence.....	195
A3. Smoking and ventilatory function	206
A4. Glossary of terms used in tables and text on smoking and ventilatory function.....	215
5. Cessation of smoking and human pulmonary function	149
A6. Epidemiological studies concerning the relationship of air pollution, social class, and smoking to chronic obstructive bronchopulmonary disease (COPD) ..	216
A7. Epidemiological studies concerning the relationship of occupational exposure and smoking to chronic obstructive bronchopulmonary disease.....	218
8. Studies concerning the relation of human pulmonary histology and smoking	155
9. Experiments concerning the effect of the inhalation of cigarette smoke upon the tracheobronchial tree and pulmonary parenchyma of animals	159
A10. Experiments concerning the effect of the chronic inhalation of NO ₂ upon the tracheobronchial tree and pulmonary parenchyma of animals	220
11. Experiments concerning the acute effect of cigarette smoke inhalation on human pulmonary function..	166
12. Experiments concerning the effect of cigarette smoke on human and animal pulmonary clearance.....	170
A13. Experiments concerning the effect of cigarette smoke or its constituents upon ciliary function	221
A14. Experiments concerning the effect of cigarette smoke on pulmonary surfactant and surface tension	225
A15. Studies concerning the relationship of smoking to infectious respiratory disease in humans	226
A16. Complications developing in the postoperative period in patients undergoing abdominal operations	230
A17. Arterial oxygen saturation before and after operation	230

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	<i>Cigarettes</i>			
				NS 30	NS 1.00 (30)			
					<10 1.67 (10)			
					10-20 3.00 (57)			
					>20 3.64 (40)			
					All 2.85 (231)			
					<i>Pipes</i>			
					NS 1.00 (30)			
					SM 1.77 (23)			
	<i>Cigars</i>							
	NS 1.00 (30)							
	SM 1.29 (18)							
Doll and Hill 1964 Great Britain (70).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	292				
					<i>Chronic bronchitis</i>			
					NS 1.00			<i>Cigarettes</i>
					1-14 6.80			NS 1.00
					15-24 12.80			1-14 0.65
					>25 21.20			15-24 1.08
					All 11.60			>25 0.63
					<i>Pipes and Cigars</i>			
					SM 3.00			All 0.81
								<i>Pipes and Cigars</i>
				SM 0.78				

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

(Actual number of deaths shown in parentheses)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 (50).	Approximately 78,000 male Canadian veterans.	Questionnaire and follow-up of death certificate.	6	124		<i>Cigarettes</i>				
						NS1.00	NS1.00	
						<107.02 (17)	<104.81 (9)	
						10-2013.65 (49)	10-206.12 (21)	
						>2014.63 (12)	>206.93 (7)	
						All11.42 (78)	All5.85 (37)	
						<i>Pipes</i>				
SM2.11 (5)	SM0.75 (2)							
<i>Cigars</i>										
SM3.57 (1)	SM3.33 (1)							
Hammond, 1966, U.S.A. (103).	440,558 males 562,671 females 35-84 years of age in 25 states.	Interviews by ACS volunteers.	4	389		<i>Males</i>				
						NS1.00 (20)	SM (age		
								45-64)	..6.55 (194)	
								SM (age		
		65-79)	..11.41 (175)							
Kahn, 1966, U.S.A. (132).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½		<i>Bronchitis</i>		<i>Current ciga- rettes only</i>			
					NS1.00 (31)	All SM	...6.49 (348)	NS1.00 (18)
					SM64	Current ciga- <i>Emphysema</i>	.10.08 (229)	1-93.63 (5)
					NS13	<i>Pipes</i>		10-204.51 (22)
					SM284	SM2.36 (9)	21-394.57 (12)
					NS18	<i>Cigars</i>		>398.31 (4)
							SM0.79 (5)	All4.49 (43)
									All14.17 (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				
						<i>Cigarettes</i>		
						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. SM1,064 NS124		<i>Cigarettes only</i>		
						NS	1.00 (124)
						1-10	2.95 (245)
						11-22	3.43 (300)
						>23	4.44 (168)
						<i>Mixed</i>		
						SM	1.55 (62)
						<i>Pipes or cigars</i>		
						SM	1.84 (289)

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 non-smoker. Such symptoms, particularly cough and sputum production, increase with increasing dosage of cigarette smoke. Table A2 also shows that pipe and cigar smokers experience COPD symptoms more frequently than nonsmokers although not to the degree found in cigarette smokers. These morbidity findings are similar to the mortality findings presented above.

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

VENTILATORY FUNCTION

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

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

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

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

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

nonsmokers (more so in the supine than in the erect position). The increase in alveolar-arterial O₂ gradients was greater for heavy than for light smokers. The authors concluded that maldistribution of ventilation and perfusion accounted for the observed hypoxemia. They also felt that this mild diffuse airway disease among asymptomatic smokers is physiologically significant mainly because of involvement of small bronchi, as expressed by maldistribution unaccompanied by gross airway obstruction. A similar ventilatory distribution abnormality among smokers has also been observed by Ross, et al. (198) with the more severe alterations found in the long-term smokers.

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

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

GENETIC FACTORS

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

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

TABLE 5.—Cessation of smoking and human pulmonary function¹

Author, year, country, reference	Number and type of population	Results		Comments		
Krumholz et al., 1965, U.S.A. (141).	10 physicians 25-33 years of age.	<i>Following 3 weeks abstinence</i>		† All subjects were >5 pack per year smokers.		
		Lung volumes—no significant change.	<i>Following 6 weeks abstinence (6 subjects only)†</i>			
		Peak expiratory flow rate—increase (p<0.01).	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.			
		Mean diffusing capacity: Resting—increase (p<0.02) Exercise—no change.				
		Compliance—increased in 6/8 tested.	Compliance—continued to show increase.			
Wilhelmsen, 1967, U.S.A. (230).	16 smokers. (43.7 mean age).	<i>Value prior to cessation</i>		<i>Significance</i> 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.	
		Vital capacity	4.50			4.57
		FEV _{1.0}	3.38			3.52
		FEV _{1.0} /FVC	75.0			76.8
		PEFR	6.97			7.45
		MEFR 50%	3.81			3.93
		MEFR 25%	1.31			1.50
		Inspiratory resistance	2.07			1.43
		Expiratory resistance	2.80			2.04
		Compliance	No change			
Peterson et al., 1968, U.S.A. (184).	12 smokers studied at various intervals and compared with 12 continuing smokers.	<i>After 1 month cessation</i>		<i>After 18 months cessation</i>		
		MBC increase (p<0.001). FEV _{1.0} increase (p<0.01).	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 alpha₁-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.

Alpha₁-antitrypsin (A₁AT).—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 alpha₁-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 A₁AT 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 A₁AT-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 A₁AT intermediate between those of normals and those with homozygous deficiency. At the present time, there is much debate about whether or not heterozygotes for A₁AT are at a greater risk of developing COPD than are A₁AT 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 A₁AT 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 non-smokers. 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).	<i>Distention of goblet cells (by percent of smoking group)</i>							The authors also noted that smokers' lungs showed shorter cilia and thicker epithelium (20 percent nonsmokers and 36 percent smokers had respiratory disease.)
			<i>None</i>	<i>Few</i>	$\frac{1}{2}$ of surface	$\frac{1}{2}$ of surface	<i>Most of surface</i>	<i>Whole surface</i>	
		NS (22)	13.6	22.7	31.8	22.7	9.1	..	
	SM (49)	12.2	10.2	10.2	18.4	26.5	22.5		
Ide et al., 1959, U.S.A. (129).	93 males autopsied within 6 hours of death. No cases of pneumonia or lung disease included.	<i>Mean thickness of tracheal and bronchial epithelium (μ) in cigarette smokers and nonsmokers</i>				<i>Mean ciliary height in trachea and bronchus on cigarette smokers and nonsmokers</i>		No cigar or pipe smokers were included.	
			<i>Trachea</i>	<i>Bronchus</i>		<i>Trachea</i>	<i>Bronchus</i>		
		NS (23)	52.8	47.7	(23)	6.39	5.95		
		Light (31)	62.0	57.5	(29)	5.62	5.49		
	Heavy (10)	66.2	61.9	(10)	4.89	4.66			
Auerbach et al., 1963, U.S.A. (17).	654 males over 60 years of age autopsied at East Orange VA Hospital.	<i>Age-standardized percentage distribution of subjects according to degree of rupture of the alveolar septums</i>							The authors also noted a dose-response relationship between smoking and degree of rupture. †None had ever smoked cigarettes regularly.
		<i>Degree of rupture</i>	<i>0-0.25</i>	<i>0.5-0.75</i>	<i>1.0-1.25</i>	<i>1.5-1.75</i>	<i>2.0-2.25</i>	<i>2.5-3.00</i>	
		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	..			

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.)	<i>Severity of emphysema (mean degree)</i>				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.
			<i>Males</i>		<i>Females</i>	
		NS (4)	1.5	(20)	1.0	(p<0.05)
		SM (35)	2.3	(12)	1.9	
Anderson et al., 1966, U.S.A. (6).	107 males and 58 females autopsied for whom smoking data was available.	<i>Percentage distribution of tobacco users in 165 necropsies by degree of emphysema severity</i>		<i>Mean severity of emphysema</i>		
				<i>Category</i>	<i>Mean Severity</i>	
		None	36 (12/33)	SM (114)	2.3	(p<0.001)
		Mild	69 (58/84)	NS (51)	0.9	
		Moderate	91 (30/33)	Male (107)	2.2	(p<0.001)
		Severe	93 (14/15)	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.	<i>Mucous gland hypertrophy</i>				
			<i>Percent</i>			
		NS	29	(2/7)	(p<0.02)	
		SM	77	(33/43)		

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
<i>Degree of tracheal and bronchial arteriolar thickening</i>							
<i>(by percentage of smokers)</i>							
		<i>0.0-0.4</i>	<i>0.5-0.9</i>	<i>1.0-1.4</i>	<i>1.5-1.9</i>	<i>2.0+</i>	
Auerbach et al., 1968, U.S.A. (14).	562 males au- topsied 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

† 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 animals¹

(Actual number of animals shown in parentheses)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results						
			Number of mice showing specified changes						
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.		<i>Number of cigarettes</i>	<i>Number of mice</i>	<i>No change</i>	<i>Mild bronchitis</i>	<i>Severe bronchitis with atypism</i>	
			<i>Months exposure</i>						
			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".	<i>Cytology of tracheobronchial mucosa</i>						
			<i>Normal</i>		<i>Focal hyperplasia</i>	<i>Generalized hyperplasia</i>	<i>Generalized emphysema</i>		
			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.		<i>Number of sections</i>	<i>Mean number of months</i>	<i>Mean parenchymal disruption/dog</i>	<i>Groups compared</i>	<i>P-value</i>	
			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 animals¹ (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. Exposed . . . (10)— <i>Early (sacrificed)</i> : 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)— <i>Early (sacrificed)</i> : 1. Alveolar space dilatation. 2. Pad-like attachments to alveolar septa. <i>Medium exposure</i> : Septal wall thickening. <i>Latest exposure</i> : 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. After 44 days — B. Up to 12 cigarettes per day for up to 423 days. C. Cigarette smoke.	Electron microscopic results: Increased number of goblet cells. Decreased number of cilia on surface lining cells. 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.

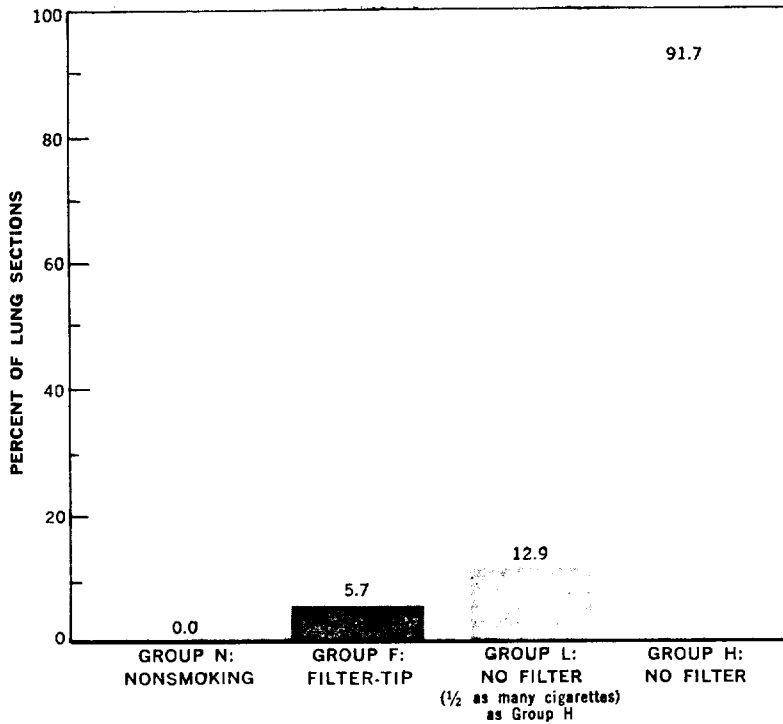


FIGURE 1.—Percent of lung sections with grade IV or V fibrosis.

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.

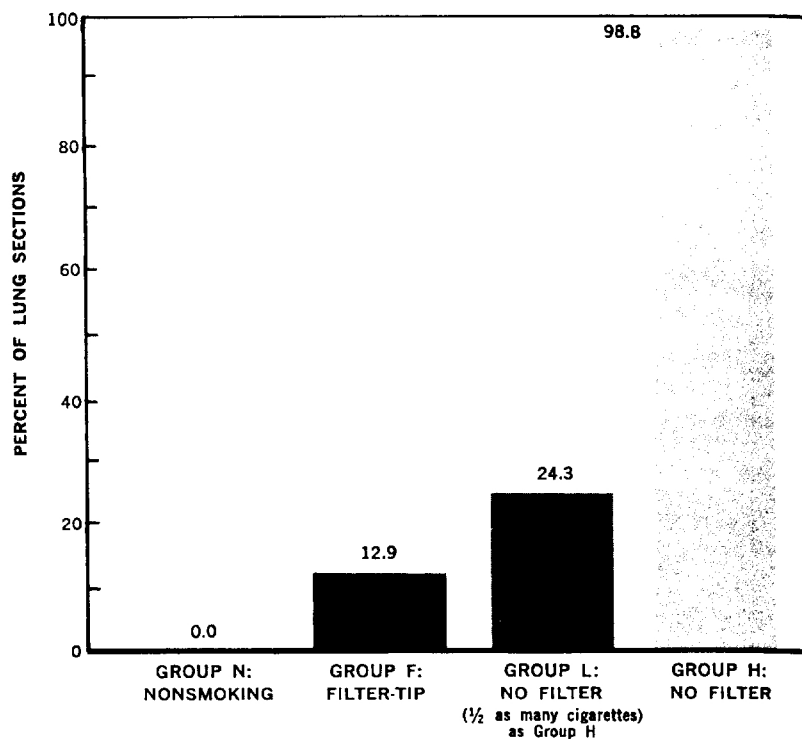


FIGURE 2.—Percent of lung sections with grade II or III emphysema.
SOURCES Hammond, et al. (104).

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 O₂ 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).	A. Pulmonary function. B. 3 cigarettes. C. 30 minutes.	<i>Vital capacity (VC)</i> I. 10/91 decrease. II. No significant change.	<i>Maximal breathing capacity</i> 10/91 decrease. No significant change.	9/91 patients showed VC increase due to clearance of secretions. All mild or moderate smokers.
	II. 20 male and 7 female normal subjects (average age 20).				
Eich, et al., 1957, U.S.A. (76).	I. 31 patients with obstructive pulmonary emphysema.	A. Esophageal balloon technique to measure pulmonary compliance and resistance.	<i>Mean airway resistance</i> I. Statistically significant increase. II. No change. III. No change.	<i>Mean airway compliance</i> No change. No change. No change.	
	II. 14 normal subjects.	B. 1 cigarette.			
	III. 5 patients with respiratory complaints. All habitual smokers.	C. Undefined.			

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

Author, year, country, reference	Number and type of population	A. Method ¹ B. Material ¹ C. Duration of smoking	Results	Comments
Attinger et al., 1958, U.S.A. (15).	I. 20 normal subjects (10 Sm, 10 NS).	A. Esophageal balloon technique to measure pulmonary compliance and resistance.	I. No change.	No change.
	II. 34 patients with various diseases; 9 rheumatic heart diseases, 8 pulmonary emphysema, 7 asthma, 5 pulmonary fibrosis, 5 undefined.	B. 1-4 cigarettes. C. 10 minute interval between cigarettes.	II. Expiratory resistance rose significantly only among patients with emphysema.	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).	<i>Pulmonary compliance</i> Significant decrease after smoking. Various groups of normals and cardiopulmonary patients showed little or no change in arterial pO ₂ during exercise and at rest following cigarette smoke inhalation.
Nadel and Comroe, 1961, U.S.A. (176).	I. 22 patients with cardiopulmonary disease—all smokers.	A. Body plethysmography. B. 15 puffs. C. 5 minutes.	<i>Airway conductance/thoracic gas volume</i>	
	II. 36 normals (21 smokers, 15 nonsmokers).		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).	A. Pulmonary function. B. 1-2 cigarettes.	<i>Mean FEV_{1.0}</i> (immediately after) I. Significant decrease. II. Significant decrease.	No significant changes observed in FEV/FVC.
	II. 15 male and 1 female pulmonary disease patients (most smokers).	C. 5-6 minutes per cigarette.		
Zamel et al., 1963, England, (240).	I. 6 male and 6 female nonsmokers.	A. Body plethysmography.	<i>Airway resistance</i> I. Significant increase. II. Significant increase.	
	II. 6 male and 6 female smokers (18-32 years of age.)	B. 1 cigarette. C. Undefined.		
Chapman, 1965, Ireland (48).	I. 12 normal volunteers (all smokers).	A. Pulmonary function Arterial blood studies.	I. All showed a decrease in diffusing capacity. II. 4/6—significant decrease in arterial O ₂ tension. No change in vital capacity or FEV.	
	II. 6 patients with chronic non-specific lung disease.	B. 1 cigarette. C. Undefined.		
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.	<i>Mean airway resistance</i> 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.	<i>FEV_{0.5}</i> No significant change	<i>Dynamic compliance</i> Significant decrease.	<i>Inspiratory and expiratory resistance</i> Significant increase
Sterling, 1967, England (213).	11 normal adults (8 smokers, 3 nonsmokers).	A. Body plethysmography. B. 15 inhalations. C. 5 minutes.		<i>Airway resistance</i> 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.	<i>Nitrogen washout time</i> Significant increase.	<i>Lung clearance index</i> Significant increase.	<i>Alveolar dilution factor</i> 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.		<i>Bronchoconstriction</i> 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.

¹All the experiments listed concern studies of pulmonary function before and after smoking the specified 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 <i>S. aureus</i> and sacrificed at intervals following exposure to various stimuli.	Significant increase in <i>S. aureus</i> retention in mice exposed to: (a) hypoxia—retention ratio 2.5 (10 percent O_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. (28).	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 FeO_2 particles measured with Scintillation counter.	<table border="1"> <thead> <tr> <th></th> <th>Number of subjects</th> <th>Average age</th> <th>50 percent clearance time (minutes)</th> <th>90 percent clearance time (minutes)</th> <th>Approximate values.</th> </tr> </thead> <tbody> <tr> <td>Nonsmokers</td> <td>9</td> <td>28</td> <td>88</td> <td>357</td> <td>None of 9 nonsmokers had 50 percent times over 200 minutes or 90 percent times over 600 minutes while</td> </tr> <tr> <td>All smokers</td> <td>14</td> <td>33</td> <td>172</td> <td>†496</td> <td>6/14 smokers exceeded both these limits.</td> </tr> <tr> <td>20-29 cigarettes/day</td> <td>7</td> <td>29</td> <td>191</td> <td>†519</td> <td></td> </tr> <tr> <td>30-40 cigarettes/day</td> <td>7</td> <td>36</td> <td>153</td> <td>†474</td> <td></td> </tr> <tr> <td>Uranium miners</td> <td>3</td> <td>52</td> <td>310</td> <td>580</td> <td></td> </tr> <tr> <td>Cigar and pipe smokers</td> <td>4</td> <td>46</td> <td>87</td> <td>375</td> <td></td> </tr> <tr> <td>Emphysema patients</td> <td>2</td> <td>66</td> <td>330</td> <td>575</td> <td></td> </tr> </tbody> </table>		Number of subjects	Average age	50 percent clearance time (minutes)	90 percent clearance time (minutes)	Approximate values.	Nonsmokers	9	28	88	357	None of 9 nonsmokers had 50 percent times over 200 minutes or 90 percent times over 600 minutes while	All smokers	14	33	172	†496	6/14 smokers exceeded both these limits.	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		
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TABLE 12.—*Experiments concerning the effect of cigarette smoke on human and animal pulmonary clearance (cont.)*

Author, year, country, reference	Subjects	Method	Results						Comments	
			<i>Average number cigarettes in 2-hour period</i>	<i>Percent clearance</i>		<i>Halftime clearance</i>		<i>Tracheal transit time</i>		
				<i>Control</i>	<i>Cigarette</i>	<i>Control</i>	<i>Cigarette</i>	<i>Control</i>	<i>Cigarette</i>	
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.	18-24 36	58 58	69 64	1.2 1.0	1.9 3.4	0.6 0.4	1.2 5.8	Those donkeys exposed to the greatest amount of smoke showed residual impairment of clearance for at least 2 months after acute exposure.
Holma, 1969, U.S.A. (125).	Rabbits (anesthetized).	Cr ⁵¹ monodisperse polystyrene aerosol.	Exposure to fresh cigarette smoke (1.5 cc. puffs, 40 puffs/8 minutes) caused a "significant" increase in lung retention 10 minutes following cessation of exposure.							

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

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

STUDIES CONCERNING THE SURFACTANT SYSTEM

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

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

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

OTHER RESPIRATORY DISORDERS

INFECTIOUS RESPIRATORY DISEASES

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

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

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

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

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

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

POSTOPERATIVE COMPLICATIONS

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

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

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

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

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

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

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

SUMMARY AND CONCLUSIONS

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

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

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

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

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

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

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

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

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

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

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

CHRONIC OBSTRUCTIVE BRONCHOPULMONARY DISEASE REFERENCES

- (1) ABBOTT, O. A., HOPKINS, W. A., VAN FLEIT, W. E., ROBINSON, J. S. A new approach to pulmonary emphysema. *Thorax* 8: 116-132, 1953.
- (2) ALBERT, R. E., LIPPMANN, M., BRISCOE, W. The characteristics of bronchial clearance in humans and the effects of cigarette smoking. *Archives of Environmental Health* 18(5): 738-755, May 1969.
- (3) ALBERT, R. E., SPIEGELMAN, J. R., SHATSKY, S., LIPPMANN, M. The effect of acute exposure to cigarette smoke on bronchial clearance in the miniature donkey. *Archives of Environmental Health* 18(1): 30-41, January 1969.
- (4) ANDERSON, A. E., JR., FURLANETO, J. A., FORAKER, A. G. Bronchopulmonary derangements in nonsmokers. *American Review of Respiratory Diseases* 101(4): 518-527, April 1970.
- (5) ANDERSON, A. E., JR., HERNANDEZ, J. A., ECKERT, P., FORAKER, A. G. Emphysema in lung macrosections correlated with smoking habits. *Science* 144(3621): 1025-1026, May 22, 1964.
- (6) ANDERSON, A. E., JR., HERNANDEZ, J. A., HOLMES, W. L., FORAKER, A. G. Pulmonary emphysema. Prevalence, severity, and anatomical patterns in macrosections, with respect to smoking habits. *Archives of Environmental Health* 12(5): 569-577, May 1966.
- (7) ANDERSON, D. O. Observations on the classification and distribution of pulmonary emphysema in Canada. *Canadian Medical Association Journal* 89: 709-716, October 5, 1963.
- (8) ANDERSON, D. O., FERRIS, B. G., JR., ZICKMANTEL, R. The Chilliwack Respiratory Survey, 1963. Part IV. The effect of tobacco smoking on the prevalence of respiratory disease. *Canadian Medical Association Journal* 92(20): 1066-1076, May 15, 1965.
- (9) ANDERSON, W. H., WILLIAMS, J. B. Effects of cigarette smoke on distribution of pulmonary perfusion. In: *Current Research in Chronic Respiratory Diseases. Proceedings of the 11th Aspen Emphysema Conference*, Aspen, Colo. U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1879, 1969. pp. 75-79.
- (10) ANTHONISEN, N. R., BASS, H., ORIOL, A., PLACE, R. E. G., BATES, D. V. Regional lung function in patients with chronic bronchitis. *Clinical Science* 35: 495-511, December 1968.
- (11) ASHFORD, J. R., BROWN, S., DUFFIELD, D. P., SMITH, C. S., FAY, J. W. J. The relation between smoking habits and physique, respiratory symptoms, ventilatory function, and radiological pneumoconiosis amongst coal workers at three Scottish collieries. *British Journal of Preventive and Social Medicine* 15: 106-117, 1961.

- (12) ASHLEY, D. J. B. Environmental factors in the aetiology of lung cancer and bronchitis. *British Journal of Preventive and Social Medicine* 23(4): 258-262, November 1969.
- (13) ATTINGER, E. O., GOLDSTEIN, M. M., SEGAL, M. S. Effects of smoking upon the mechanics of breathing. I. In normal subjects. *American Review of Tuberculosis and Pulmonary Diseases* 77(1): 1-16, January 1958.
- (14) AUERBACH, O., HAMMOND, E. C., GARFINKEL, L., Thickening of walls of arterioles and small arteries in relation to age and smoking habits. *New England Journal of Medicine* 278(18): 980-984, May 2, 1968.
- (15) AUERBACH, O., HAMMOND, E. C., KIRMAN, D., GARFINKEL, L. Emphysema produced in dogs by cigarette smoking. *Journal of the American Medical Association* 199(4): 241-246, January 23, 1967.
- (16) AUERBACH, O., HAMMOND, E. C., KIRMAN, D., GARFINKEL, L. Emphysema produced in dogs by cigarette smoking. In: Hanna, M. G., Jr., Nettesheim, P., Gilbert, J. R. (Editors). *Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. U.S. Atomic Energy Commission Symposium Series 18, April 1970. pp. 375-387.*
- (17) AUERBACH, O., STOUT, A. P., HAMMOND, E. C., GARFINKEL, L. Smoking habits and age in relation to pulmonary changes. Rupture of alveolar septums, fibrosis and thickening of walls of small arteries and arterioles. *New England Journal of Medicine* 269(20): 1045-1054, November 14, 1963.
- (18) AVIADO, D. M., CARRILLO, L. R. Hormones and pulmonary effects of tobacco. I. Corticosteroids and their antiasthmatic action. *Archives of Environmental Health* 18(6): 925-933, June 1969.
- (19) AVIADO, D. M., PALECEK, F. Pulmonary effects of tobacco and related substances. I. Pulmonary compliance and resistance in the anesthetized dog. *Archives of Environmental Health* 15(2): 187-193, August 1967.
- (20) AVIADO, D. M., SADAVONGVIVAD, C., CARRILLO, L. R. Cigarette smoke and pulmonary emphysema. Influence of bronchodilators and biogenic amines in experimental induction in rats. *Archives of Environmental Health* 20(4): 483-487, April 1970.
- (21) AVIADO, D. M., SAMANEK, M. Bronchopulmonary effects of tobacco and related substances. I. Bronchoconstriction and bronchodilatation: Influence of lung denervation. *Archives of Environmental Health* 11(2): 141-151, August 1965.
- (22) AVIADO, D. M., SAMANEK, M., FOLLE, L. E. Cardiopulmonary effects of tobacco and related substances. I. The release of histamine during inhalation of cigarette smoke and anoxemia in the heart-lung and intact dog preparation. *Archives of Environmental Health* 12(6): 705-724, June 1966.
- (23) BAIR, W. J., DILLEY, J. V. Pulmonary clearance of $^{59}\text{Fe}_2\text{O}_3$ and $^{51}\text{Cr}_2\text{O}_3$ in rats and dogs exposed to cigarette smoke. In: Davies, C. N. (Editor). *Inhaled Particles and Vapors. II. Proceedings of an International Symposium. Cambridge, September 28 to October 1, 1965, Oxford, Pergamon Press, 1967. pp. 251-271.*
- (24) BALCHUM, O. J., FELTON, J. S., JAMISON, J. N., GAINES, R. S., CLARKE, D. R., OWAN, D., THE INDUSTRIAL HEALTH COMMITTEE, THE TUBERCULOSIS AND HEALTH ASSOCIATION OF LOS ANGELES COUNTY. A Survey for chronic respiratory disease in an industrial city. Preliminary results. *American Review of Respiratory Diseases* 86(5): 675-685, November 1962.

- (25) BALLENGER, J. J. Experimental effect of cigarette smoke on human respiratory cilia. *New England Journal of Medicine* 263(17) : 832-835, October 27, 1960.
- (26) BALLENGER, J. J., DAWSON, F. W., DERUYTER, M. G., HARDING, H. B. Effects of nicotine on ciliary activity *in vitro*. *Annals of Otology, Rhinology and Laryngology* 74(2) : 303-311, June 1965.
- (27) BATES, D. V., GORDON, C. A., PAUL, G. I., PLACE, R. E. G., SNIDAL, D. P., WOOLF, C. R. Chronic bronchitis. Report on the third and fourth stages of the coordinated study of chronic bronchitis in the Department of Veterans Affairs, Canada. *Medical Services Journal, Canada* 22(1) : 1-59, January 1966.
- (28) BATTISTA, S. P., KENSLER, C. J. Use of the nonimmersed *in vitro* chicken tracheal preparation for the study of ciliary transport activity. Cigarette smoke and related components. *Archives of Environmental Health* 20(3) : 318-325, March 1970.
- (29) BATTISTA, S. P., KENSLER, C. J. Mucus production and ciliary transport activity. *In vivo* studies using the chicken. *Archives of Environmental Health* 20(3) : 326-338, March 1970.
- (30) BEST, E. W. R. A Canadian Study of Smoking and Health. Ottawa, Department of National Health and Welfare, 1966. 137 pp.
- (31) BICKERMAN, H. A., BARACH, A. L. The effect of cigarette smoking on ventilatory function in patients with bronchial asthma and obstructive pulmonary emphysema. *Journal of Laboratory and Clinical Medicine* 43(3) : 455-462, March 1954.
- (32) BLAIR, W. H., HENRY, M. C., EHRLICH, R. Chronic toxicity of nitrogen dioxide. II. Effect on histopathology of lung tissue. *Archives of Environmental Health* 18(2) : 186-192, February 1969.
- (33) BOAKE, W. C. A Study of illness in a group of Cleveland families. XVIII. Tobacco smoking and respiratory infections. *New England Journal of Medicine* 259(26) : 1245-1249, December 25, 1958.
- (34) BONNELL, J. A. Emphysema and proteinuria in men casting copper-cadmium alloys. *British Journal of Industrial Medicine* 12: 181-195, July 1955.
- (35) BONNELL, J. A., KAZANTZIS, G., KING, E. A follow-up study of men exposed to cadmium oxide fume. *British Journal of Industrial Medicine* 16: 135-147, 1959.
- (36) BOUCOT, K. R., COOPER, D. A., WEISS, W. Smoking and the health of older men. I. Smoking and chronic cough. *Archives of Environmental Health* 4(1) : 59-72, January 1962.
- (37) BOUHUYS, A. PETERS, J. M. Control of environmental lung disease. *New England Journal of Medicine* 283(11) : 573-582, September 10, 1970.
- (38) BOUHUYS, A., SCHILLING, R. S. F., VAN DE WOESTIJNE, K. P. Cigarette smoking, occupational dust exposure, and ventilatory capacity. *Archives of Environmental Health* 19(6) : 793-797, December 1969.
- (39) BOUHUYS, A., WOLFSON, R. L., HORNER, D. W., BRAIN, J. D., ZUSKIN, E. Byssinosis in cotton textile workers. Respiratory survey of a mill with rapid labor turnover. *Annals of Internal Medicine* 71(2) : 257-269, August 1969.
- (40) BOUSHY, S. F., HELGASON, A. H., BILLIG, D. M., GYORKY, F. G. Clinical physiologic, and morphologic examination of the lung in patients with bronchogenic carcinoma and the relation of the findings to postoperative deaths. *American Review of Respiratory Diseases* 101(5) : 685-695, May 1970.

- (41) BOWER, G. Respiratory symptoms and ventilatory function in 172 adults employed in a bank. *American Review of Respiratory Diseases* 83: 684-689, 1961.
- (42) BRINKMAN, G. L., COATES, E. O., JR. The prevalence of chronic bronchitis in an industrial population. *American Review of Respiratory Diseases* 86: 47-54, 1962.
- (43) BROWN, K. E., CAMPBELL, A. H. Tobacco, alcohol and tuberculosis. *British Journal of Diseases of the Chest* 55(3): 150-158, 1961.
- (44) CARSON, S., GOLDHAMER, R., CARPENTER, R. Responses of ciliated epithelium to irritants. Mucus transport in the respiratory tract. *American Review of Respiratory Diseases* 93 (3, Part 2): 86-92, March 1966.
- (45) CEDERLOF, R., FRIBERG, L., HRUBEC, Z. Cardiovascular and respiratory symptoms in relation to tobacco smoking. *Archives of Environmental Health* 18(6): 934-940, June 1969.
- (46) CEDERLOF, R., FRIBERG, L., JONSSON, E., KAIJ, L. Respiratory symptoms and "angina pectoris" in twins with reference to smoking habits. An epidemiological study with mailed questionnaire. *Archives of Environmental Health* 13(6): 726-737, December 1966.
- (47) CHANG, S. C. Microscopic properties of whole mounts and sections of human bronchial epithelium of smokers and nonsmokers. *Cancer* 10(6): 1246-1262, November-December 1957.
- (48) CHAPMAN, T. T. The acute effect of cigarette smoking on pulmonary function. *Journal of the Irish Medical Association* 56(333): 72-74, March 1965.
- (49) CHESTER, E. H., GILLESPIE, D. G., KRAUSE, F. D. The prevalence of chronic obstructive pulmonary disease in chlorine gas workers. *American Review of Respiratory Diseases* 99(3): 365-373, March 1969.
- (50) CHEVALIER, R. B., KRUMHOLZ, R. A., ROSS, J. C. Reaction of nonsmokers to carbon monoxide inhalation. Cardiopulmonary responses at rest and during exercise. *Journal of the American Medical Association* 198(10): 1061-1064, December 5, 1966.
- (51) CHIANG, S. T., WANG, B. C. Acute effects of cigarette smoking on pulmonary function. *American Review of Respiratory Diseases* 101(6): 860-868, June 1970.
- (52) CHIVERS, C. P. Respiratory function and disease among workers in alkaline dusts. *British Journal of Industrial Medicine* 16: 51-60, 1959.
- (53) COATES, E. O., JR. BOWER, G. C., REINSTEIN, N. Chronic respiratory disease in postal employees. Epidemiologic survey of a group employed in one building. *Journal of the American Medical Association* 191(3): 161-166, January 18, 1965.
- (54) COHEN, J. Chronic bronchitis and emphysema. Observations on trends and distribution according to death certificate data, Israel 1960 to 1964. *Israel Journal of Medical Sciences* 3(6): 885-889, November-December 1967.
- (55) COLLEGE OF GENERAL PRACTITIONERS. Chronic bronchitis in Great Britain. A national survey carried out by the respiratory diseases study group of the College of General Practitioners. *British Medical Journal* 2: 973-979, October 14, 1961.
- (56) COMROE, J. H., JR., FORSTER, R. E., II, DUBOIS, A. B., BRISCOE, W. A., CARLSEN, E. *The Lung. Clinical Physiology and Pulmonary Function Tests*. Chicago, Year Book Medical Publishers, Inc., 1963. 390 pp.
- (57) COOK, W. A., WEBB, W. R. Surfactant in chronic smokers. *Annals of Thoracic Surgery* 2(3): 327-333, May 1966.

- (58) COOLEY, J. R. T., REID, D. D. Urban and social origins of childhood bronchitis in England and Wales. *British Medical Journal* 2(5703) : 213-217, April 25, 1970.
- (59) DALHAMN, T. The effect of cigarette smoke on ciliary activity in the upper respiratory tract. *A.M.A. Archives of Otolaryngology* 70 : 166-168, 1959.
- (60) DALHAMN, T. Effect of cigarette smoke on ciliary activity. *American Review of Respiratory Diseases* 93(3) : 108-114, March 1966.
- (61) DALHAMN, T., RYLANDER, R. Ciliastatic action of smoke from filter-tipped and non-tipped cigarettes. *Nature* 201(4917) : 401-402, January 25, 1964.
- (62) DALHAMN, T., RYLANDER, R. Ciliastatic action of cigarette smoke. Varying exposure times. *Archives of Otolaryngology* 81(4) : 379-382, April 1965.
- (63) DALHAMN, T., RYLANDER, R. Tar content and ciliotoxicity of cigarette smoke. *Acta Pharmacologica et Toxicologica* 25(3) : 369-372, 1967.
- (64) DALHAMN, T., RYLANDER, R. Ciliotoxicity of cigarette smoke and its volatile components. *American Review of Respiratory Diseases* 98(3) : 509-511, September 1968.
- (65) DALHAMN, T., RYLANDER, R. Ciliotoxicity of cigar and cigarette smoke. *Archives of Environmental Health* 20(2) : 252-253, February 1970.
- (66) DAVIS, T. R. A., BATTISTA, S. P., KENSLER, C. J. Mechanism of respiratory effects during exposure of guinea pigs to irritants. *Archives of Environmental Health* 15(4) : 412-419, October 1967.
- (67) DEANE, M., GOLDSMITH, J. R., TUMA, D. Respiratory conditions in outside workers. Report on outside plant telephone workers in San Francisco and Los Angeles. *Archives of Environmental Health* 10(2) : 323-331, February 1965.
- (68) DENSEN, P. M., JONES, E. W., BASS, H. E., BREUER, J. A survey of respiratory disease among New York City postal and transit workers. 1. Prevalence of symptoms. *Environmental Research* 1 : 262-286, 1967.
- (69) DENSEN, P. M., JONES, E. W., BASS, H. E., BREUER, J., REED, E. A survey of respiratory disease among New York City postal and transit workers. 2. Ventilatory function test results. *Environmental Research* 2(4) : 277-296, July 1969.
- (70) DOLL, R., HILL, A. B. Mortality in relation to smoking: Ten years' observations of British doctors. (Part I) *British Medical Journal* 1(5395) : 1399-1410, May 30, 1964.
- (71) DOLL, R., HILL, A. B. Mortality in relation to smoking: Ten years' observations of British doctors. (Concluded) *British Medical Journal* 1(5396) : 1460-1467, June 6, 1964.
- (72) DOWLING, H. F., JACKSON, G. G., INOUE, T. Transmission of the experimental common cold in volunteers. II. The effect of certain host factors upon susceptibility. *Journal of Laboratory and Clinical Medicine* 50(4) : 516-525, October 1957.
- (73) EDELMAN, N. H., MITTMAN, C., NORRIS, A. H., COHEN, B. H., SHOCK, N. W. The effects of cigarette smoking upon spirometric performance of community dwelling men. *American Review of Respiratory Diseases* 94(3) : 421-429, September 1966.
- (74) EDWARDS, F., MCKEOWN, T., WHITFIELD, A. G. W. Association between smoking and disease in men over sixty. *Lancet* 1 : 196-200, January 24, 1959.
- (75) EHRLICH, R., HENRY, M. C., FENTERS, J. Influence of nitrogen dioxide on resistance to respiratory infections. In: Hanna, M. G., Jr., Nette-

- sheim, P., Gilbert, J. R. (Editors). *Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. U.S. Atomic Energy Commission Symposium Series 18, April 1970. pp. 243-257.*
- (76) EICH, R. H., GILBERT, R., AUCHINCLOSS, J. H., JR. The acute effects of smoking on the mechanics of respiration in chronic obstructive pulmonary emphysema. *American Review of Tuberculosis* 76: 22-32, 1957.
- (77) ELWOOD, P. C., PEMBERTON, J., MERRETT, J. D., CAREY, G. C. R., MCAULAY, I. R. Byssinosis and other respiratory symptoms in flax workers in Northern Ireland. *British Journal of Industrial Medicine* 22:27-37, 1965.
- (78) ERIKSSON, S. Studies in Alpha₁-antitrypsin Deficiency. *Acta Medica Scandinavica* 177 (Supplementum 432): 1965. 85 pp.
- (79) FALK, G. A., BRISCOE, W. A. Chronic obstructive pulmonary disease and heterozygous alpha₁-antitrypsin deficiency. *Annals of Internal Medicine* 72(4): 595-596, April 1970.
- (80) FALK, H. L., TREMER, H. M., KOTIN, P. Effect of cigarette smoke and its constituents on ciliated mucus-secreting epithelium. *Journal of the National Cancer Institute* 23(5): 999-1012, November 1959.
- (81) FERRIS, B. G., JR., ANDERSON, D. O. The prevalence of chronic respiratory disease in a New Hampshire town. *American Review of Respiratory Diseases* 86(2): 165-177, August 1962.
- (82) FERRIS, B. G., JR., ANDERSON, D. O., BURGESS, W. A. Prevalence of respiratory disease in a flax mill in the United States. *British Journal of Industrial Medicine* 19: 180-185, 1962.
- (83) FINKLEA, J. F., SANDIFER, S. H., SMITH, D. D. Cigarette smoking and epidemic influenza. *American Journal of Epidemiology* 90(5): 390-399, November 1969.
- (84) FLETCHER, C. M., HORN, D. Smoking and health. *WHO Chronicle* 24(8): 345-370, August 1970.
- (85) FLETCHER, C. M., TINKER, C. M. Chronic bronchitis. A further study of simple diagnostic methods in a working population. *British Medical Journal* 1: 1491-1498, May 27, 1961.
- (86) FLICK, A. L., PATON, R. R. Obstructive emphysema in cigarette smokers. *A.M.A. Archives of Internal Medicine* 104: 518-526, 1959.
- (87) FRANKLIN, W., LOWELL, F. C. Unrecognized airway obstruction associated with smoking. A probable forerunner of obstructive pulmonary emphysema. *Annals of Internal Medicine* 54(3): 379-386, March 1961.
- (88) FRASCA, J. M., AUERBACH, O., PARKS, V. R., JAMIESON, J. D. Electron microscopic observations of the bronchial epithelium of dogs. II. Smoking dogs. *Experimental and Molecular Pathology* 9(3): 380-399. December 1968.
- (89) FREEMAN, G., CRANE, S. C. STEPHENS, R. J., FURIOSI, N. J. Pathogenesis of the nitrogen dioxide-induced lesion in the rat lung: A review and presentation of new observations. *American Review of Respiratory Diseases* 98(3): 429-443, September 1968.
- (90) FREEMAN, G., HAYDON, G. B. Emphysema after low-level exposure to NO₂. *Archives of Environmental Health* 8(1): 125-128, January 1964.
- (91) FREEMAN, G., STEPHENS, R. J., CRANE, S. C., FURIOSI, N. J. Lesion of the lung in rats continuously exposed to two parts per million of nitrogen dioxide. *Archives of Environmental Health* 17(2): 181-192, August 1968.

- (92) FREOUR, P., COUDRAY, P., ROUSSEL, A., SERISE, A. Les bronchites chroniques et l'insuffisance respiratoire dans l'agglomération de Bordeaux. (Chronic bronchitis and respiratory insufficiency in Bordeaux). *Journal de Medecine de Bordeaux* 143(2) : 1865-1879, December 1966.
- (93) GANDEVIA, B. A productive cough upon request as an index of chronic bronchitis: The effects of age, sex, smoking habit, and environment upon prevalence in Australian general practice. *Medical Journal of Australia* 1(1) : 16-20, January 4, 1969.
- (94) GIAMMONA, S. T. Effects of cigarette smoke and plant smoke on pulmonary surfactant. *American Review of Respiratory Diseases* 96(3) : 539-541, September 1967.
- (95) GOLDSMITH, J. R., HECHTER, H. H., PERKINS, N. M. BORHANI, N. O. Pulmonary function and respiratory findings among longshoremen. *American Review of Respiratory Diseases* 86(6) : 867-874, December 1962.
- (96) GREEN, G. M., CAROLIN, D. The depressant effect of cigarette smoke on the *in vitro* antibacterial activity of alveolar macrophages. *New England Journal of Medicine* 276(8) : 421-427, February 23, 1967.
- (97) GREENBERG, M., MILNE, J. F., WATT, A. Survey of workers exposed to dusts containing derivatives of *Bacillus subtilis*. *British Medical Journal* 2 : 629-633, June 13, 1970.
- (98) GUENTER, C. A., WELCH, M. H., RUSSELL, T. R., HYDE, R. M., HAMMARSTEN, J. F. The pattern of lung disease associated with alpha-1 antitrypsin deficiency. *Archives of Internal Medicine* 122(3) : 254-257, September 1968.
- (99) GUILLERM, R., SAINDELLE, A., FALOT, P., HEE, J. Action de la fumee de cigarette et de quelquesuns de ses constituants sur les resistances ventilatoires chez le cobaye. (Action of cigarette smoke and some of its constituents on ventilatory resistance in the guinea pig.) *Archives Internationales de Pharmacodynamie et de Therapie* 167(1) : 101-114, May 1967.
- (100) GUYATT, A. R., BERRY, G., ALPERS, J. H., BRAMLEY, A. C., FLETCHER, C. M. Relationship of airway conductance and its immediate change on smoking to smoking habits and symptoms of chronic bronchitis. *American Review of Respiratory Diseases* 101(1) : 44-54, January 1970.
- (101) HAMMARSTEN, J. F., WELCH, M. H., RICHARDSON, R. H., PATTERSON, C. D., GUENTER, C. A. Familial alpha₁-antitrypsin deficiency and pulmonary emphysema. *Transactions of the American Clinical and Climatological Association* 80(1) : 7-14, 1968.
- (102) HAMMOND, E. C. Evidence on the effects of giving up cigarette smoking. *American Journal of Public Health and the Nation's Health* 55(5) : 682-691, May 1965.
- (103) HAMMOND, E. C. Smoking in relation to the death rates of 1 million men and women. In: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966, pp. 127-204.
- (104) HAMMOND, E. C., AUERBACH, O., KIRMAN, D., GARFINKEL, L. Effects of cigarette smoking on dogs. I. Design of experiment, mortality, and findings in lung parenchyma. *Archives of Environmental Health* 21(6) : 740-753, December 1970.
- (105) HAMMOND, E. C., HORN, D. Smoking and death rates—report on forty-four months of follow-up of 187,783 men. II. Death rates by cause.

- Journal of the American Medical Association 166(11): 1294-1308, March 15, 1958.
- (106) HAYDON, G. B., DAVIDSON, J. T., LILLINGTON, G. A., WASSERMAN, K. Nitrogen dioxide-induced emphysema in rabbits. *American Review of Respiratory Diseases* 95(5): 797-805, May 1967.
- (107) HAYDON, G. B., FREEMAN, G., FURIOSI, N. J. Covert pathogenesis of NO₂ induced emphysema in the rat. *Archives of Environmental Health* 11(6): 776-783, December 1965.
- (108) HAYNES, W. F., JR., KRSTULOVIC, V. J., BELL, A. L. L., JR. Smoking habit and incidence of respiratory tract infections in a group of adolescent males. *American Review of Respiratory Diseases* 93(5): 730-735, May 1966.
- (109) HENRY, M. C., FINDLAY, J., SPANGLER, J., EHRLICH, R. Chronic toxicity of NO₂ in squirrel monkeys. III. Effect on resistance to bacterial and viral infection. *Archives of Environmental Health* 20(5): 566-570, May 1970.
- (110) HEPPER, N. G., HYATT, R. E., FOWLER, W. S. Detection of chronic obstructive lung disease. An evaluation of the medical history and physical examination. *Archives of Environmental Health* 19(6): 806-813, December 1969.
- (111) HERNANDEZ, J. A., ANDERSON, A. E., JR., HOLMES, W. L., FORAKER, A. G. Pulmonary parenchymal defects in dogs following prolonged cigarette smoke exposure. *American Review of Respiratory Diseases* 93(1): 78-83, January 1966.
- (112) HIGGINS, I. T. T. Respiratory symptoms, bronchitis and ventilatory capacity in random sample of an agricultural population. *British Medical Journal* 2: 1198-1203, November 23, 1957.
- (113) HIGGINS, I. T. T. Tobacco smoking, respiratory symptoms, and ventilatory capacity. Studies in random samples of the population. *British Medical Journal* 1: 325-329, February 7, 1959.
- (114) HIGGINS, I. T. T., COCHRAN, J. B. Respiratory symptoms, bronchitis and disability in a random sample of an agricultural community in Dumfriesshire. *Tubercle* 39: 296-301, 1958.
- (115) HIGGINS, I. T. T., COCHRANE, A. L. Chronic respiratory disease in a random sample of men and women in the Rhondda Fach in 1958. *British Journal of Industrial Medicine* 18: 93-102, 1961.
- (116) HIGGINS, I. T. T., COCHRANE, A. L., GILSON, J. C., WOOD, C. H. Population studies of chronic respiratory disease. A comparison of miners, foundryworkers, and others in Staveley, Derbyshire. *British Journal of Industrial Medicine* 16: 255-268, 1959.
- (117) HIGGINS, I. T. T., GILSON, J. C., FERRIS, B. G., JR., WATERS, M. E., CAMPBELL, H., HIGGINS, M. W. Chronic respiratory disease in an industrial town: A nine-year follow-up study. Preliminary report. *American Journal of Public Health and the Nation's Health* 58(9): 1667-1676, September 1968.
- (118) HIGGINS, I. T. T., HIGGINS, M. W., LOCKSHIN, M. D., CANALE, N. Chronic respiratory disease in mining communities in Marion County, West Virginia. *British Journal of Industrial Medicine* 25(3): 165-175, July 1968.
- (119) HIGGINS, I. T. T., OLDHAM, P. D., COCHRANE, A. L., GILSON, J. C. Respiratory symptoms and pulmonary disability in an industrial town. Survey of a random sample of the population. *British Medical Journal* 2: 904-909, October 20, 1956.

- (120) HILDING, A. C. On cigarette smoking, bronchial carcinoma and ciliary action. II. Experimental study on the filtering action of cow's lungs, the deposition of tar in the bronchial tree and removal by ciliary action. *New England Journal of Medicine* 254(25): 1155-1160, June 21, 1956.
- (121) HOLLAND, W. W., ELLIOTT, A. Cigarette smoking, respiratory symptoms and anti-smoking propaganda. An experiment. *Lancet* 1(7532): 41-43, January 6, 1968.
- (122) HOLLAND, W. W., HALIL, T., BENNETT, A. E., ELLIOTT, A. Indications for measures to be taken in childhood to prevent chronic respiratory disease. *Milbank, Memorial Fund Quarterly* 47 (3, part 2): 215-227, July 1969.
- (123) HOLLAND, R. H., KOZLOWSKI, E. J., BOOKER, L. The effect of cigarette smoke on the respiratory system of the rabbit. A final report. *Cancer* 16(5): 612-615, May 1963.
- (124) HOLLAND, W. W., REID, D. D. The urban factor in chronic bronchitis. *Lancet* 1(7383): 445-448, February 27, 1965.
- (125) HOLMA, B. The acute effect of cigarette smoke on the initial course of lung clearance in rabbits. *Archives of Environmental Health* 18(2): 171-173, February 1969.
- (126) HUHTI, E. Prevalence of Respiratory Symptoms, Chronic Bronchitis and Pulmonary Emphysema in a Finnish Rural Population. Field survey of age group 40-64 in the Harjavalta area. *Acta Tuberculosea et Pneumologica Scandinavica (Supplementum 61)*: 1965. 111 pp.
- (127) HURST, A. Familial emphysema. *American Review of Respiratory Diseases* 80: 179-180, 1959.
- (128) HYATT, R. E., KISTIN, A. D., MAHAN, T. K. Respiratory disease in Southern West Virginia coal miners. *American Review of Respiratory Diseases* 89(3): 387-401, March 1964.
- (129) IDE, G., SUNTZEFF, V., COWDRY, E. V. A comparison of the histopathology of tracheal and bronchial epithelium of smokers and nonsmokers. *Cancer* 12(3): 473-484, May-June, 1959.
- (130) ITO, H., AVIADO, D. M. Pulmonary emphysema and cigarette smoke. Experimental induction and use of bronchodilators in rats. *Archives of Environmental Health* 16(6): 865-870, June 1968.
- (131) JAMES, R. H. Prior smoking as a determinant of the distribution of pulmonary ventilation. *American Review of Respiratory Diseases* 101(1): 105-107, January 1970.
- (132) KAHN, H. A. The Dorn study of smoking and mortality among U.S. veterans: Report on 8½ years of observation. In: Haenzel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966, pp. 1-125.
- (133) KAMINSKI, E. J., FANCHER, O. E., CALANDRA, J. C. *In vivo* studies of the ciliastatic effects of tobacco smoke. Absorption of ciliastatic components by wet surfaces. *Archives of Environmental Health* 16(2): 188-193, February 1968.
- (134) KENNEDY, J. R., ELLIOTT, A. M. Cigarette smoke: The effect of residue on mitochondrial structure. *Science* 168(3935): 1097-1098, May 29, 1970.
- (135) KENSLER, C. J., BATTISTA, S. P. Chemical and physical factors affecting mammalian ciliary activity. *American Review of Respiratory Diseases* 93(3, Part 2): 93-102, March 1966.

- (136) KLEINERMAN, J. Effects of NO₂ in hamsters: Autoradiographic and electron microscopic aspects. In: Hanna, M. G., Jr., Nettesheim, P., Gilbert, J. R. (Editors). Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. U.S. Atomic Energy Commission Symposium Series 18, April 1970. pp. 271-281.
- (137) KORDIK, P., BULBRING, E., BURN, J. H. Ciliary movement and acetylcholine. *British Journal of Pharmacology and Chemotherapy* 7: 67-79, 1952.
- (138) KRAHL, V. E., BULMASH, M. H. Studies on living ciliated epithelium. *American Review of Respiratory Diseases* 99(5): 711-718, May 1969.
- (139) KRUGER, A. P., SMITH, R. F. Effects of gaseous ions on tracheal ciliary rate. Proceedings of the Society for Experimental Biology and Medicine 98: 412-414, 1958.
- (140) KRUMHOLZ, R. A., CHEVALIER, R. B., ROSS, J. C. Cardiopulmonary function in young smokers. A comparison of pulmonary function measurements and some cardiopulmonary responses to exercise between a group of young smokers and a comparable group of nonsmokers. *Annals of Internal Medicine* 60(4): 603-610, April 1964.
- (141) KRUMHOLZ, R. A., CHEVALIER, R. B., ROSS, J. C. Changes in cardiopulmonary functions related to abstinence from smoking. Studies in young cigarette smokers at rest and exercise at 3 and 6 weeks of abstinence. *Annals of Internal Medicine* 62(2): 197-207, February 1965.
- (142) KRUMHOLZ, R. A., CHEVALIER, R. B., ROSS, J. C. A comparison of pulmonary compliance in young smokers and nonsmokers. *American Review of Respiratory Diseases* 92(1): 102-107, July 1965.
- (143) KUEPPERS, F. Identification of the heterozygous state for the alpha₁-antitrypsin deficiency gene in man. *Biochemical Genetics* 3(3): 283-288, 1969.
- (144) KUEPPERS, F., FALLAT, R., LARSON, R. K. Obstructive lung disease and alpha₁-antitrypsin deficiency gene heterozygosity. *Science* 165(3896): 899-901, August 29, 1969.
- (145) LABELLE, C. W., BEVILACQUA, D. M., BRIEGER, H. The influence of cigarette smoke on lung clearance. An experimental approach. *Archives of Environmental Health* 12(5): 588-596, May 1966.
- (146) LAMBERT, P. M., REID, D. D. Smoking, air pollution, and bronchitis in Britain. *Lancet* 1(7652): 853-857, April 25, 1970.
- (147) LARSON, R. K., BARMAN, M. L. The familial occurrence of chronic obstructive pulmonary disease. *Annals of Internal Medicine* 63(6): 1001-1008, December 1965.
- (148) LARSON, R. K., BARMAN, M. L., KUEPPERS, F., FUDENBERG, H. H. Genetic and environmental determinants of chronic obstructive pulmonary disease. *Annals of Internal Medicine* 72(5): 627-632, May 1970.
- (149) LAURENZI, G. A., GUARNERI, J. J., ENDRIGA, R. B., CAREY, J. P. Clearance of bacteria by the lower respiratory tract. *Science* 142: 1572-1573, December 20, 1963.
- (150) LEESE, W. L. B. An investigation into bronchitis. *Lancet* 2: 762-765, October 13, 1956.
- (151) LEFCOE, N. M., WONNACOTT, T. H. The prevalence of chronic respiratory disease in the male physicians of London, Ontario. *Canadian Medical Association Journal* 102(9): 381-385, February 28, 1970.
- (152) LEUCHTENBERGER, C., LEUCHTENBERGER, R., ZEBRUN, W., SHAFFER, P. A correlated histological, cytological, and cytochemical study of the tracheobronchial tree and lungs of mice exposed to cigarette smoke.

- II. Varying responses of major bronchi to cigarette smoke, absence of bronchogenic carcinoma after prolonged exposure, and disappearance of bronchial lesions after cessation of exposure. *Cancer* 13(4) : 721-732, July-August 1960.
- (153) LEWIS, G. P., LYLE, H., MILLER, S. Association between elevated hepatic water-soluble protein-bound cadmium levels and chronic bronchitis and/or emphysema. *Lancet* 2(7634) : 1330-1333, December 20, 1969.
- (154) LIEBERMAN, J. Heterozygous and homozygous alpha₁-antitrypsin deficiency in patients with pulmonary emphysema. *New England Journal of Medicine* 281(6) : 279-284, August 7, 1969.
- (155) LIEBERMAN, J., MITTMAN, C., SCHNEIDER, A. S. Screening for homozygous and heterozygous alpha₁-antitrypsin deficiency. Protein electrophoresis on cellulose acetate membranes. *Journal of the American Medical Association* 210(11) : 2055-2060, December 15, 1969.
- (156) LIEBESCHUETZ, H. J. Respiratory signs and symptoms in young soldiers and their relationship to smoking. *Journal of the Royal Army Medical Corps* 105 : 76-81, 1959.
- (157) LOWE, C. R. An association between smoking and respiratory tuberculosis. *British Medical Journal* 2 : 1081-1086, November 10, 1956.
- (158) LOWE, C. R. Chronic bronchitis and occupation. Joint meeting No. 1. Section of Occupational Medicine with Section of Epidemiology and Preventive Medicine. Proceedings of the Royal Society of Medicine 61(1) : 98-102, January 1968.
- (159) LUNDMAN, T. Smoking in Relation to Coronary Heart Disease and Lung Function in Twins. A Co-twin Study. *Acta Medica Scandinavica* 180 (Supplement 455) : 1966. 75 pp.
- (160) MCDERMOTT, M., COLLINS, M. M. Acute effects of smoking on lung airways resistance in normal and bronchitic subjects. *Thorax* 20 : 562-569, 1965.
- (161) MARTT, J. M. Pulmonary diffusing capacity in cigarette smokers. *Annals of Internal Medicine* 56(1) : 39-45, January 1962.
- (162) MASIN, F., MASIN, M. Frequencies of alveolar cells in concentrated sputum specimens related to cytologic classes. *Acta Cytologica* 10(5) : 362-367, September-October 1966.
- (163) MEGAHED, G. E., SENNA, G. A., EISSA, M. H., SALEH, S. Z., EISSA, H. A. Smoking versus infection as the aetiology of bronchial mucous gland hypertrophy in chronic bronchitis. *Thorax* 22(3) : 271-278, May 1967.
- (164) MENDENHALL, W. L., SHREEVE, K. E. The effect of cigarette smoke on the tracheal cilia. (Abstract) 28th Annual Meeting, April 21-24, 1937, Memphis, Tennessee. The Scientific Proceedings of the American Society for Pharmacology and Experimental Therapeutics, Inc. *Journal of Pharmacology and Experimental Therapeutics* 60 : 111-112, 1937.
- (165) MILLER, D., BONDURANT, S. Effects of cigarette smoke on the surface characteristics of lung extracts. *American Review of Respiratory Diseases* 85(5) : 692-696, May 1962.
- (166) MILLER, J. M., SPROULE, B. J. Acute effects of inhalation of cigarette smoke on mechanical properties of the lungs. *American Review of Respiratory Diseases* 94(5) : 721-726, November 1966.
- (167) MILLS, C. A. Tobacco smoking: Some hints of its biologic hazards. *Ohio State Medical Journal* 46(12) : 1165-1170, December 1950.
- (168) MITCHELL, R. S., WEBB, N. C., FILLEY, G. F. Chronic obstructive bronchopulmonary disease. III. Factors influencing prognosis. *American Review of Respiratory Diseases* 89(6) : 878-896, June 1964.

- (169) MITCHELL, R. S., SILVERS, G. W., DART, G. A., PETTY, T. L., VINCENT, T. N., RYAN, S. F., FILLEY, G. F. Clinical and morphologic correlations in chronic airway obstruction. *American Review of Respiratory Diseases* 97(1) : 54-61, January 1968.
- (170) MORIYAMA, I. M., DAWBER, T. R., KANNEL, W. B. Evaluation of diagnostic information supporting medical certification of deaths from cardiovascular disease. In: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966. pp. 405-419.
- (171) MORK, T. A Comparative Study of Respiratory Disease in England and Wales and Norway. *Acta Medica Scandinavica* 172 (Supplementum 384), 1962. 100 pp.
- (172) MORTON, A. Postoperative hypoxaemia. *Medical Journal of Australia* 2(7) : 341-342, August 16, 1969.
- (173) MORTON, H. J. V. Tobacco smoking and pulmonary complications after operation. *Lancet* 1: 368-370, March 18, 1944.
- (174) MOTLEY, H. L., KUZMAN, W. J. Cigarette smoke. Its effect on pulmonary function measurements. *California Medicine* 88(3) : 211-220, March 1958.
- (175) MYRVIK, Q. N., EVANS, D. G. Metabolic and immunologic activities of alveolar macrophages. *Archives of Environmental Health* 14(1) : 92-96, January 1967.
- (176) NADEL, J. A., COMROE, J. H., JR. Acute effects of inhalation of cigarette smoke on airway conductance. *Journal of Applied Physiology* 16: 713-716, 1961.
- (177) NANDI, M., JICK, H., SLONE, D., SHAPIRO, S., LEWIS, G. P. Cadmium content of cigarettes. *Lancet* 2(7634) : 1329-1330, December 20, 1969.
- (178) OSWALD, N. C., MEDVEL, V. C. Chronic bronchitis; the effect of cigarette-smoking. *Lancet* 2: 843-844, October 22, 1955.
- (179) PALECEK, F., AVIADO, D. M. Pulmonary effects of tobacco and related substances. II. Comparative effects of cigarette smoke, nicotine, and histamine on the anesthetized cat. *Archives of Environmental Health* 15(2) : 194-203, August 1967.
- (180) PALECEK, F., OSKOUI, M., AVIADO, D. M. Pulmonary effects of tobacco and related substances. III. Inhibition of synthesis of histamine in various species. *Archives of Environmental Health* 15(2) : 204-213, August 1967.
- (181) PARNELL, J. L., ANDERSON, D. O., KINNIS, C. Cigarette smoking and respiratory infections in a class of student nurses. *New England Journal of Medicine* 274(8) : 979-984, May 5, 1966.
- (182) PETERS, J. M., FERRIS, B. G., JR. Smoking, pulmonary functions and respiratory symptoms in a college-age group. *American Review of Respiratory Diseases* 95(5) : 774-782, May 1967.
- (183) PETERS, J. M., FERRIS, B. G., JR. Smoking and morbidity in a college-age group. *American Review of Respiratory Diseases* 95(5) : 783-789, May 1967.
- (184) PETERSON, D. I., LONERGAN, L. H., HARDINGE, M. G. Smoking and pulmonary function. *Archives of Environmental Health* 16(2) : 215-218, February 1968.
- (185) PHILLIPS, A. M., PHILLIPS, R. W., THOMPSON, J. L. Chronic cough. Analysis of etiologic factors in a survey of 1,274 men. *Annals of Internal Medicine* 45(2) : 216-231, August 1956.

- (186) PIPER, D. W. Respiratory complications in the postoperative period. *Scottish Medical Journal* 3(5) : 193-198, May 1958.
- (187) PRATT, S. A., FINLEY, T. N., SMITH, M. H., LADMAN, A. J. A comparison of alveolar macrophages and pulmonary surfactant (?) obtained from the lungs of human smokers and nonsmokers by endobronchial lavage. *Anatomical Record* 163(4) : 497-508, April 1969.
- (188) RAKIETEN, N., RAKIETEN, M. L., FELDMAN, D., BOYKIN, M. J., JR. Mammalian ciliated respiratory epithelium. Studies with particular reference to effects of menthol, nicotine, and smoke of mentholated and nonmentholated cigarettes. *A.M.A. Archives of Otolaryngology* 56: 494-503, 1942.
- (189) RANKIN, J., GEE, J. B., CHOSY, L. W. The influence of age and smoking on pulmonary diffusing capacity in healthy subjects. *Medicina Thoracalis* 22(3) : 366-374, 1965.
- (190) RANKIN, J. G., HALE, G. S., WILKINSON, P., O'DAY, D. M., SANTAMARIA, J. N., BABARCZY, G. Relationship between smoking and pulmonary disease in alcoholism. *Medical Journal of Australia* 1(14) : 730-733, April 5, 1969.
- (191) READ, J., SELBY, T. Tobacco smoking and ventilatory function of the lungs. *British Medical Journal* 2: 1104-1108, October 28, 1961.
- (192) REVOTSKIE, N., KANNEL, W., GOLDSMITH, J. R., DAWER, T. R. Pulmonary function in a community sample. *American Review of Respiratory Diseases* 86(6) : 907-911, December 1962.
- (193) RIMINGTON, J. Chronic bronchitis, smoking and social class. A study among working people in the towns of Mid and East Cheshire. *British Journal of Diseases of the Chest* 63(4) : 193-205, 1969.
- (194) ROBERTSON, D. G., WARRELL, D. A., NEWTON-HOWES, J. S., FLETCHER, C. M. Bronchial reactivity to cigarette and cigar smoke. *British Medical Journal* 3(5665) : 269-271, August 2, 1969.
- (195) ROQUE, A. L., PICKREN, J. W. Enzymatic changes in fluorescent alveolar macrophages of the lungs of cigarette smokers. *Acta Cytologica* 12(6) : 420-429, November-December 1968.
- (196) ROSENKRANTZ, H., ESBER, H. J., SPRAGUE, R. Lung hydroxyproline levels in mice exposed to cigarette smoke. *Life Sciences* 8(11, Part 1) : 571-576, June 1, 1969.
- (197) ROSENKRANTZ, H., SPRAGUE, R. Biochemical screen to investigate whole smoke and vapor phase effects in mice. *Archives of Environmental Health* 18(6) : 917-924, June 1969.
- (198) ROSS, J. C., LEY, G. D., KRUMHOLZ, R. A., RAHBARI, H. A technique for evaluation of gas mixing in the lung: Studies in cigarette smokers and nonsmokers. *American Review of Respiratory Diseases* 95(3) : 447-454, March 1967.
- (199) SAMANEK, M., AVIADO, D. M. Bronchopulmonary effects of tobacco and related substances. II. Bronchial arterial injections of nicotine and histamine. *Archives of Environmental Health* 11(2) : 152-159, August 1965.
- (200) SAMANEK, M., AVIADO, D. M. Bronchopulmonary effects of tobacco and related substances. IV. Bronchial vascular and bronchomotor responses; their suggested defense function. *Archives of Environmental Health* 11(2) : 167-176, August 1965.
- (201) SAMANEK, M., AVIADO, D. M. Cardiopulmonary effects of tobacco and related substances. III. Pulmonary vascular effects of cigarette smoke and nicotine. *Archives of Environmental Health* 12(6) : 717-724, June 1966.

- (202) SAMANEK, M., AVIADO, D. M., PESKIN, G. W. Bronchopulmonary effects of tobacco and related substances. III. Axon reflexes elicited from the visceral pleura. *Archives of Environmental Health* 11(2) : 160-166, August 1965.
- (203) SCARPELLI, E. M. *The Surfactant System of the Lung*. Philadelphia, Lea & Febiger, 1968. 269 pp.
- (204) SCHOETTLIN, C. E. The health effect of air pollution on elderly males. *American Review of Respiratory Diseases* 86(6) : 878-897, December 1962.
- (205) SHAH, J. R., WARAWADEKAR, M. S., DESHMUKH, P. A., PHUTANE, P. N. Institutional survey of pulmonary tuberculosis with special reference to smoking habits. *Indian Journal of Medical Sciences* 13(5) : 381-392, May 1959.
- (206) SHORT, J. J., JOHNSON, H. J., LEY, H. A., JR. The effects of tobacco smoking on health. A study of 2,031 medical records. *Journal of Laboratory and Clinical Medicine* 24 : 586-589, 1939.
- (207) SIMONSSON, B. Effect of cigarette smoking on the forced expiratory flow rate. *American Review of Respiratory Diseases* 85 : 534-539, 1962.
- (208) SLUIS-CREMER, G. K., SICHEL, H. S. Ventilatory functions in males in a Wit-watersrand town. Comparison between smokers and nonsmokers. *American Review of Respiratory Diseases* 98(2) : 229-239, August 1968.
- (209) SLUIS-CREMER, G. K., WALTERS, L. G., SICHEL, H. S. Chronic bronchitis in miners and nonminers: An epidemiological survey of a community in the gold-mining area in the Transvaal. *British Journal of Industrial Medicine* 24(1) : 1-12, January 1967.
- (210) SMITH, J. P., SMITH, J. C., MCCALL, A. J. Chronic poisoning from cadmium fume. *Journal of Pathology and Bacteriology* 80 : 287-296, 1960.
- (211) SPURGASH, A., EHRLICH, R., PETZOLD, R. Effect of cigarette smoke on resistance to respiratory infection. *Archives of Environmental Health* 16(3) : 385-391, March 1968.
- (212) STANESCU, D. C., TECULESCU, D. B., PACURARU, R., GAVRILESCU, N. Chronic effect of smoking upon pulmonary distribution of ventilation in healthy males. *Respiration* 25(6) : 497-504, 1968.
- (213) STERLING, G. M. Mechanism of bronchoconstriction caused by cigarette smoking. *British Medical Journal* 3 : 275-277, July 29, 1967.
- (214) STRIEDER, D. J., MURPHY, R., KAZEMI, H. Mechanism of postural hypoxemia in asymptomatic smokers. *American Review of Respiratory Diseases* 99(5) : 760-766, May 1969.
- (215) TALAMO, R. C., ALLEN, J. D., KAHAN, M. G., AUSTEN, K. F. Hereditary alpha₁-antitrypsin deficiency. *New England Journal of Medicine* 278(7) : 345-351, February 15, 1968.
- (216) TARKOFF, M. P., KUEPPERS, F., MILLER, W. F. Pulmonary emphysema and alpha₁-antitrypsin deficiency. *American Journal of Medicine* 45(2) : 220-228, August 1968.
- (217) THURLBECK, W. M., HENDERSON, J. A., FRASER, R. G., BATES, D. V. Chronic obstructive lung disease. A comparison between clinical, radiogenologic, functional and morphologic criteria in chronic bronchitis, emphysema, asthma and bronchiectasis. *Medicine* 49(2) : 81-115, March 1970.
- (218) TOKUHATA, G. K., DESSAUER, P., PENDERGRASS, E. P., HARTMAN, T., DIGON, E., MILLER, W. Pneumoconiosis among anthracite coal miners in Pennsylvania. *American Journal of Public Health and the Nation's Health* 60(3) : 441-451, March 1970.

- (219) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. 1968 Supplement to the 1967 Public Health Review. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1968. 117 pp.
- (220) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Cigarette smoking and health characteristics, United States, July 1964-June 1965. Washington, U.S. Department of Health, Education, and Welfare, Vital and Health Statistics Series 10, No. 34, Public Health Service Publication No. 1000, May 1967. 64 pp.
- (221) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Vital Statistics of the United States—1967. Vol. II—Mortality, Part A. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication, 1969.
- (222) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Vital Statistics Rates in the United States 1940-1960. Washington, U.S. Department of Health, Education and Welfare, Public Health Service Publication No. 1677, 1968. 881 pp.
- (223) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.
- (224) WEBB, W. R., COOK, W. A., LANIUS, J. W., SHAW, R. R. Cigarette smoke and surfactant. *American Review of Respiratory Diseases* 95(2) : 244-247, February 1967.
- (225) WEIR, J. M., DUNN, J. E., JR. Smoking and mortality: A prospective study. *Cancer* 25(1) : 105-112, January 1970.
- (226) WELCH, M. H., REINECKE, M. E., HAMMARSTEN, J. F., GUENTER, C. A. Antitrypsin deficiency in pulmonary disease: The significance of intermediate levels. *Annals of Internal Medicine* 71(3) : 533-542, September 1969.
- (227) WICKEN, A. J. Environmental and personal factors in lung cancer and bronchitis mortality in Northern Ireland, 1960-62. Tobacco Research Council, Research Paper No. 9, 1966. 84 pp.
- (228) WIGHTMAN, J. A. K. A prospective survey of the incidence of postoperative pulmonary complications. *British Journal of Surgery* 55(2) : 85-91, February 1968.
- (229) WIKLANDER, O., NORLIN, U. Effect of physiotherapy on post-operative pulmonary complications: A clinical and roentgenographic study of 200 cases. *Acta Chirurgica Scandinavica* 112: 246-254, 1957.
- (230) WILHELMSSEN, L. Effects on bronchopulmonary symptoms, ventilation, lung mechanics of abstinence from tobacco smoking. *Scandinavian Journal of Respiratory Diseases* 48(3/4) : 407-414, 1967.
- (231) WILHELMSSEN, L., OHRA, I., TIBBLIN, G. Decrease in ventilatory capacity between ages of 50 and 54 in representative sample of Swedish men. *British Medical Journal* 3(5670) : 553-556, September 6, 1969.
- (232) WILSON, R. H., MEADOR, R. S., JAY, B. E., HIGGINS, E. The pulmonary pathologic physiology of persons who smoke cigarettes. *New England Journal of Medicine* 262(19) : 956-961, May 12, 1960.
- (233) WINKELSTEIN, W., KANTOR, S. Respiratory symptoms and air pollution in an urban population of Northeastern United States. *Archives of Environmental Health* 18(5) : 760-777, May 1969.
- (234) WOOLCOCK, A. J., VINCENT, N. J., MACKLEM, P. T. Frequency dependence of compliance as a test for obstruction in the small airways. *Journal of Clinical Investigation* 48: 1097-1105, 1969.

- (235) WYNDER, E. L., GOODMAN, D. A., HOFFMANN, D. Ciliotoxic components in cigarette smoke. II. Carboxylic acids and aldehydes. *Cancer* 18(4): 505-509, April 1965.
- (236) WYNDER, E. L., KAISER, H. E., GOODMAN, D. A., HOFFMANN, D. A method for determining ciliastatic components in cigarette smoke. *Cancer* 16(9): 1222-1225, September 1963.
- (237) WYNDER, E. L., KAUFMAN, P. L., LESSER, R. L. A short-term follow-up study on ex-cigarette smokers. With special emphasis on persistent cough and weight gain. *American Review of Respiratory Diseases* 96(4): 645-655, October 1967.
- (238) WYNDER, E. L., LEMON, F. R., MANTEL, N. Epidemiology of persistent cough. *American Review of Respiratory Diseases* 91(5): 679-700, May 1965.
- (239) YEAGER, H., JR. Alveolar cells: Depressant effect of cigarette smoke on protein synthesis. *Proceedings of the Society for Experimental Biology and Medicine* 131(1): 247-250, May 1969.
- (240) ZAMEL, N., YOUSSEF, H. H., PRIME, F. J. Airway resistance and peak expiratory flow-rate in smokers and nonsmokers. *Lancet* 1: 1237-1238, June 8, 1963.
- (241) ZWI, S., GOLDMAN, H. I., LEVIN, A. Cigarette smoking and pulmonary function in healthy young adults. *American Review of Respiratory Diseases* 89(1): 73-81, January 1964.

BRONCHOPULMONARY

APPENDIX TABLES

TABLE A2.—*Smoking and chronic obstructive pulmonary disease symptoms¹—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.					<i>Chronic Bronchitis</i> <i>Males</i> NS 15.8 (474) SM 18.4 (1,940) <i>Females</i> 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.		<i>Cough and sputum</i> <i>Males</i> NS 7.1 (28) SM 53.9 (222) <i>Females</i> NS 4.5 (176) SM 17.2 (93)	<i>Males</i> NS 7.1 SM 19.8 <i>Females</i> NS 21.6 SM 9.7	<i>Males</i> NS 3.6 SM 17.1 <i>Females</i> NS 9.7 SM 15.1	<i>Chronic Bronchitis</i> <i>Males</i> NS 3.6 SM 9.9 <i>Females</i> NS 3.4 SM 8.6	

TABLE A2.—*Smoking and chronic obstructive pulmonary disease symptoms¹—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.)		<i>Females</i> <i>Cough and sputum</i> NS (6) SM 24.0 (75) NS 3.1 (64) SM 3.0 (20)	<i>Males</i> NS 33.3 SM 29.3 <i>Females</i> NS 45.3 SM 20.0	<i>Males</i> NS 0.0 SM 16.0 <i>Females</i> NS 10.9 SM 10.0	<i>Chronic bronchitis</i> <i>Males</i> NS 0.0 SM 6.7 <i>Females</i> NS 0.0 SM 5.0	
Edwards et al., 1959, England (74).	1,737 male out- patients on lists of general prac- titioners >60 years of age.					<i>Chronic bronchitis</i> 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 cardio- pulmonary 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 (188)		
Higgins et al., 1959, England (116).	776 males in various occupations 25-64 years of age.		<i>Cough and sputum</i> SM 7.1 (85) NS 36.9 (575)	NS 9.4 SM 24.9	NS 7.1 SM 20.2	<i>Chronic bronchitis</i> SM 14.3 NS 3.5	

TABLE A2.—Smoking and chronic obstructive pulmonary disease symptoms¹—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 (118).	393 males in various occupations 55-64 years of age.		<i>Cough and sputum</i>			<i>Chronic bronchitis</i>	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.
			NS 6.1 (33)	NS 18.2	NS 3.0	NS 0.0	
			1-14 g./day 9.7 (173)	1-14 g./day 30.1	1-14 g./day 23.7	1-14 g./day 13.9	
		>15 42.3 (142)	>15 33.8	>15 23.9	>15 17.6		
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.					<i>Respiratory symptoms</i>	Respiratory symptoms—"bronchitis and/or asthma". No dose relationship found.
						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)			

TABLE A2.—*Smoking and chronic obstructive pulmonary disease symptoms¹—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)	NS 20.4		NS 34.7		Chest illness—chest colds during each of last 2 winters.
		SM 27.6 (76)	SM 34.2		SM 38.2		
		Pipe, cigar .. (13)	Pipe, cigar 15.4		Pipe, cigar 53.9		
Fletcher and Tinker, 1961, England (85).	363 male London transport employees 40-50 years of age.	NS (30)	NS 8.7	NS	NS 4.3		
		1-14 g./day 15.5 (156)	1-14 g./day .. 29.9	1-14 g./day .. 8.2	1-14 g./day .. 8.2		
		>15 27.3 (116)	>15 36.9	>15 8.6	>15 10.7		
Read and Selby, 1961, Australia (191).	170 male and 132 female individuals interviewed in an out-patient clinic (not all patients).	<i>Males</i>					
		NS 4.4					
		SM 23.1					
		EX 21.2					
		<i>Females</i>					
		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)	NS 11.0	NS 9.8			
		SM 23.3 (1,198)	SM 30.4	SM 14.5			
		<1 pack-year 11.0 (257)	<1 pack-year 12.0	<1 pack-year 10.0			
		1- 9 17.0 (263)	1- 9 18.0	1- 9 12.0			
		10-19 25.0 (303)	10-19 32.0	10-19 18.0			
		20-29 21.0 (236)	20-29 34.0	20-29 21.0			
		30-39 28.0 (144)	30-39 40.0	30-39 13.0			
		40-49 39.0 (92)	40-49 37.0	40-49 38.0			
		50-59 34.0 (29)	50-59 45.0	50-59 29.0			
		>60 50.0 (24)	>60 62.0				

TABLE A2.—Smoking and chronic obstructive pulmonary disease symptoms¹—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. (86).	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.					<i>Chronic Nonspecific Respiratory Disease</i> 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.					<i>Chronic bronchitis</i> 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 (87) 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.					<i>Respiratory conditions</i> NS 31.4 (744) Moderate/heavy smokers 43.0 (1,238)	
Coates et al., 1965, U.S.A. (58).	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)			<i>Cough and chronic phlegm</i> 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.					<i>Persistent cough, phlegm, dyspnea</i> 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.	<i>Males</i> NS 4.1 (122) EX 8.5 (141) 1-14 31.5 (108) 15-24 40.8 (191) >25 42.4 (85) <i>Females</i> NS 4.5 (709) EX 13.3 (30) 1-14 10.4 (77) 15-24 43.0 (6) >25 (1)	<i>Males</i> NS 10.7 EX 17.7 1-14 38.0 15-24 42.9 >25 42.4 <i>Females</i> NS 5.9 EX 13.3 1-14 10.4 15-24 } 57.0 >25 }	<i>Males</i> NS 15.6 EX 24.8 1-14 25.0 15-24 26.2 >25 31.8 <i>Females</i> NS 29.2 EX 33.3 1-14 14.3 15-24 } 14.0 >25 }		<i>Chronic bronchitis</i> <i>Males</i> NS 5.7 EX 16.3 1-14 38.0 15-24 41.4 >25 40.0 <i>Females</i> NS 4.5 EX 13.3 1-14 10.4 15-25 } 57.0 >25 }	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 symptoms¹—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.	<i>New York City</i>					
		NS 14.0 (44)					
		Pipe, cigar 33.0 (54)					
		Cigarettes:					
		1-10 . . . 45.0 (44)					
		10-20 . . . 46.0 (88)					
		>20 . . . 67.0 (85)					
		<i>California</i>					
		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.					<i>Clinical signs of bronchitis and respiratory insufficiency</i>	
						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.					<i>Average number of severe respiratory illnesses per 10 students (adjusted for age)</i>	Heavy smoker—more than 10 cigarettes per day.
						NS 0.36	
						All smokers 2.30	
						Heavy SM 3.34	

TABLE A2.—*Smoking and chronic obstructive pulmonary disease symptoms¹—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.	<i>Postal</i>		<i>Postal</i>		<i>Postal</i>		
		NS	7.0 (903)	13.1	19.8		Dyspnea represented by Grade II only.	
		Pipe, cigar	12.4 (628)	17.4	24.8			
		Cigarettes only	27.0 (2,687)	28.9	31.7			
		<i>Transit</i>		<i>Transit</i>		<i>Transit</i>		
		NS	6.4 (1,012)	9.5	11.7			
Pipe, cigar	10.5 (765)	14.1	14.2					
	Cigarettes only	23.5 (3,745)	23.7	21.9				
Higgins et al., 1968, U.S.A. (118).	926 white male resi- dents of Marion County, West Virginia, 26-69 years of age.	NS	15.4 (162)	NS	31.1	NS	5.0	
		SM	47.2 (513)	SM	46.2	SM	10.7	
		EX	19.3 (144)	EX	28.5	EX	16.8	
Holland and Elliott, 1968, England (121).	9,786 male and female school children.	<i>Males</i>		<i>Females</i>				
		NS	3.8 (1,900)	3.2 (3,137)	2.4	2.1		
		SM	6.3 (1,098)	6.3 (554)	6.1	8.3		
		EX	2.9 (1,782)	4.3 (1,151)	3.9	4.2		
		<1 cigarette/day	5.8 (876)	5.8 (876)		5.8		
		1-2	6.5 (417)	6.5 (417)		8.4		
3-4	5.6 (124)	5.6 (124)		8.1				
>5	9.9 (142)	9.9 (142)		18.3				

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

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

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

Author, year, country, reference	Number and type of population	Cough	Sputum production	Breathlessness or dyspnea	Chest illnesses	Other	Comments	
Gandevia 1969	762 male and 1,304 female patients	<i>Males</i>					Productive cough upon request.	
Australia (93).	from 13 general practices in all parts of Australia.	NS10.3 (234)					
		SM51.3 (528)					
		<i>Females</i>						
		NS10.5 (857)					
		SM37.4 (447)					
Rimington 1969	41,729 male and 22,295 female persons participating in mass miniature radiography screening.					<i>Age-adjusted total prevalence of chronic bronchitis</i>	Cigarette dosage gradient significant to p<0.001.	
England (193).						<i>Males</i>		
						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
						<i>Females</i>		
						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	
Wilhelmsen et al., 1969, Sweden (231).	313 males 50-54 years of age randomly sampled from population of Göteborg.					<i>Chronic bronchitis</i>		
						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 symptoms¹—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).	<i>Persistent cough and phlegm</i>						
			<i>Males</i>					
			<i>Age</i>	<i>Age</i>	<i>Age</i>	<i>Age</i>		
			<i>35-45</i>	<i>45-55</i>	<i>55-65</i>	<i>65-69</i>		
		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)		
			<i>Females</i>					
		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.					<i>Age-standardized rates of chronic respiratory disease</i>	Excluded from ex-smokers are those cigarette smokers who now smoke pipes or cigars.	
						NS	1.0 (88)	
						EX	5.0 (61)	
						SM	34.0 (101)	
						Pipe, cigar	12.0 (33)	

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

TABLE A2a.—*Smoking and chronic obstructive pulmonary disease symptoms¹—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		Bronchitis		Comments		
		<i>Observed/ expected cases</i>	<i>Hyper morbidity ratio</i>	<i>Observed expected cases</i>	<i>Hyper morbidity ratio</i>			
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 hyper morbidity 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 avail- able).	<i>Prevalence of respiratory symptoms</i>				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	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.	Cigarettes/day:		<i>Height-in-inches</i>			†Mean EFR in liters per minute. Regression analysis of data revealed a significant relationship between smoking and decreasing function.
			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	87 (157)				
	>15 grams	.140 (193)	87 (157)				
		.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.	<i>RV/TLC</i>					
		NS	SM	NS	SM	NS	SM
		5.69 (14)	4.44 (14)	21.1	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.			<i>FEV_{1.0}</i>			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.				
				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)									
Fletcher and Tinker, 1961, England (85).	363 male London transport employees.		<i>Mean peak EFR</i>								
			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.			<i>FEV_{1.0}</i>			Heavy smoker represents an amount equal to or more than 30 pack years.				
				Heavy	2,670			3,011	2,710	Light	3,703 (59)
				Light	2,489			2,656	2,284	Heavy	3,578 (104)

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 indus- try.	<i>MMEFR</i>						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.
		NS	15.5 (38)	7.8 (19)			
		Pack/year:						
		<1	15.0 (257)	8.0			
		1-9	10.0 (263)	6.0			
		10-19	...	10.0 (303)	12.0			
		20-29	...	19.0 (236)	24.0			
		30-39	...	33.0 (144)	26.0			
40-49	...	38.0 (92)	40.0					
50-59	...	55.0 (29)	45.0					
>60	71.0 (24)	62.0					
Goldsmith et al., 1962, U.S.A. (95).	3,311 active or retired longshore- men.	<i>MEFR</i>			<i>FEV_{1.0}</i>			Authors concluded that cigarette smoke was found to have a slight effect on pulmonary function.
		NS	313.63 (250)	2.99			
		Pipe, cigar	299.26 (125)	2.80			
		EX	295.23 (102)	2.84			
		Cigarettes/day:						
		≤20	309.73 (144)	2.89			
20-40	...	303.44 (346)	2.91					
≥40	307.63 (57)	2.90					
Martt, 1962, U.S.A. (161).	73 healthy medical per- sonnel with- out signifi- cant age difference between smokers and nonsmokers.				<i>D_LCO</i>		Smokers defined as those smoking >20 cigarettes/ day for varying periods.	
		NS	33.10 (30)				
		SM <5 years	...	28.40 (8)				
		5-10 years	...	28.20 (10)				
>10 years	...	24.90 (25)						

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.			<i>FEV_{1.0}</i>			Data presented in terms of ratio of observed to predicted values.			
				<i>Males</i>	<i>Females</i>					
				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)						
Krumholz et al., 1964, U.S.A. (140).	18 physicians 24-37 years of age.	<i>MEFR</i>			<i>Mean D_L</i>					
				NS	580 (9)	NS	SM			
				SM	1590 (9)	Rest	36	31		
				Exercise:						
						2 minutes	.50	41		
				4 minutes	.50	43				
				3 minutes post exercise	39	35				
Zwi et al., 1964, U.S.A. (241).	20 medical students or graduate physicians.	<i>MMEFR</i>						Authors found a significant difference between SM and NS for RV/TLC, compliance, and non-elastic resistance.		
				NS	187 (10)	4.34	5.77			
				SM	193 (10)	15.09	15.53			
Coates et al., 1965, U.S.A. (53).	1,342 male and 242 female post office employees >40 years of age.			<i>FEV_{1.0}</i>		<i>Timed VC'</i>		<i>FEV_{1.0}/VC</i>		
				<i>NS</i>	<i>>25 cig/day</i>	<i>NS</i>	<i>>25/day</i>	<i>NS</i>	<i>>25/day</i>	
				Age:						
				40-44	2.99 (186)	2.85 (69)	3.89	3.85	0.77	0.74
				45-49	2.95 (170)	2.64 (42)	3.92	3.83	0.74	0.70
				50-54	2.75 (115)	2.62 (22)	3.71	3.74	0.74	0.70
		55-59	2.64 (64)	2.44 (18)	3.54	3.61	0.74	0.68		
		60-64	2.35 (53)	2.30 (8)	3.30	3.33	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 ₁ †	VC	Miscellaneous	Comments		
Huhti, 1966, Finland (186).	653 male and 823 female residents of a rural region in Finland.	NS EX	PEFR†		Forced VC†	Miscellaneous	Pipe and cigar smokers not included. † Difference between NS and >25/day is significant for 45-49, 60-64 age groups. ‡ Trend is not statistically significant.		
			Males	Females				Males	Females
			569 (122)	410 (709)				4.40	3.18
			551 (141)	403 (30)				4.51	3.19
			Cigarettes/day:						
1-14	431 (77)	4.40	3.53						
15-24	518 (108)	3.17	2.74	4.40	3.53				
>25	537 (191)	3.30	2.82	4.51	3.50				
		517 (85)	3.08	4.26					
Krumholz et al., 1965, U.S.A. (148).	20 male medical students or graduate physicians.	NS SM	Pulmonary compliance		Mean body surface area for 2 groups was not significantly different. Smokers are those with equal to or greater than 5 pack year history.	Miscellaneous	Comments		
			NS	SM				NS	SM
			0.241 (10)	0.177 (10)					
			Compliance/FRC						
			NS	SM					
			0.054	0.042					
Rankin et al., 1965, U.S.A. (189).	125 males without a past history of respiratory disease 20-63 years of age.	NS SM	FEV ₁ †		NS SM	D _L D _L	NS includes pipe and cigar smokers and ex-smokers of greater than 1 pack year. D _L values have been corrected for COHb.		
			NS	SM				NS	SM
			106.6	102.7				31.1	25.9
			102.7	102.7				6.22	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)	7.89	<i>FEV</i> _{1.0} 2.83	<i>Vital capacity</i> 4.93		Ex-smokers of cigarettes only. Difference significant between NS and current cigarette smokers at p<0.01.	
		Current cigarette smokers. ² 151 (118)		² 2.64				² 4.74
		EX 157 (93)		2.80				4.77
		Pipe, cigar . . 167 (47)		2.91				5.08
Peters and Ferris, 1967, U.S.A. (182).	124 male college age students.	<i>MEFR</i>		<i>FEV</i> _{1.0} 4.63	<i>FEV</i> _{1.0} / <i>VC</i> ² 87.5		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.	
		NS ² 10.28 (41)	4.59					85.3
		Moderate . . 10.06 (54)	4.43					83.9
		EX 9.48 (10)	4.74					83.2
Higgins et al., 1968, U.S.A. (118).	926 white male residents of Marion County, West Virginia, 20-69 years of age.			<i>FEV</i> _{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.	NS	Grams/day:	35-44	45-54	>55	<i>FEV</i> _{1.0}				1 cigarette = 1 gram. 1 ounce tobacco = 26 grams. 1 cigar = 2 to 5 grams. † Derived slopes found significantly different from 0.				
				553 (106)	527 (101)	444 (27)	35-44	45-54	>55						
				1-14	557 (26)	519 (17)	410 (7)	3.70	3.22			2.76			
				15-24	532 (94)	446 (35)	401 (13)	3.64	3.31			2.24			
				>25	†528 (66)	†494 (31)	†380 (10)	3.66	2.94			2.28			
				3.54	3.05	†2.12									
Stanescu et al., 1968, Rumania (212).	87 male bus drivers; 27 aged 20-25, 60 aged 40-60, all without respiratory symptoms.	NS		<i>FEV</i> _{1.0}		Younger	Older	Younger	Older	<i>Nitrogen gradient</i>					
				4,470 (14)	3,310 (40)					5,125	4,290	Younger	Older		
				SM	4,500 (13)					†3,200 (20)	†5,285	†4,290	†1.47	†3.77	
Densen et al., 1969, U.S.A. (69).	5,287 male postal and transit workers in New York City.	NS		<i>FEV</i> _{1.0}			White	Non-white				FEV expressed as standardized for specified postal and transit workers at age 45 and at sitting height of 35 inches. Includes mixed smokers.			
				<i>Postal</i>		Transit							White	Non-white	
				All cigarette	3.29 (685)										3.05 (204)
				<25 grams/day	3.11 (2,340)										2.94 (768)
				≥25 grams/day	3.14 (1,292)										2.95 (599)
					3.06 (1,038)										2.93 (161)
					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)

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.			<i>FEV</i> _{1.0}			FEV expressed as percent of predicted value for age, sex, and height.
			NS	97.5 (12)			
				SM	78.4 (58)		
Wilhelmsen et al., 1969, Sweden (231).	313 male residents of Göteborg 50-54 years of age.			<i>PEFR</i>	<i>FEV</i> _{1.0}	<i>VC</i>	1963 values only.
			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	
Lefcoe and Wonnacott, 1970, Canada (151).	310 male physicians of London, Ontario.		<i>MMFR</i>	<i>FEV</i> _{1.0}			MMFR has been standardized for age and height.
			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		

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.	<u>FEV_{1.0}</u> 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.	<u>N₂ washout gradient</u> Significant differences between smoking dis- cordant 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-discor- dant 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 ₂ O.....	Volume change of the lung produced by a unit pressure change.
RV.....	Residual volume.....	Liters.....	Volume of gas remaining in the lungs at the end of a maximal expiration.
TLC.....	Total lung capacity.....	Liters.....	Volume of gas contained in the lungs at the end of a maximal inspiration.
FRC.....	Functional residual capacity.	Liters.....	Volume of gas remaining in the lungs at the resting expiratory level.
	Alveolar volume.....	Liters.....	Volume of gas contained in pulmonary alveoli.

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

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

Author, year, country, reference	Number and type of population	Results
Higgins, 1957, England (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 transport 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 NO₂ 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).	<i>In vitro</i> : 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).	<i>In vitro</i> : (a) rabbit and rat tracheal rings. (b) human nasal mucous membrane	I. Nicotine in Locke-Ringers solution. II. Cigarette smoke in solution.	I. Ciliary activity depressed only upon exposure to 100 mg. percent solution. II. Ciliary activity depressed after 15–20 minutes exposure depending on concentration of smoke in solution.
Kordik et al., 1952, England (187).	<i>In vitro</i> : 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).	<i>In vitro</i> : Cow trachea	Cigarette smoke (direct exposure).	All tracheas showed depressed or absent ciliary activity.
Krueger and Smith, 1958, U.S.A. (139).	<i>In vivo</i> : Rabbit trachea	Cigarette smoke.	Cigarette smoke decreased ciliary activity by approximately 200 beats/minute.
Dalhamn, 1959, Sweden (59).	<i>In vivo</i> : I. Rat trachea <i>In vitro</i> : 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).	<i>In vitro</i> : 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).	<i>In vitro</i> : 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).	<i>In vivo:</i> 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).	<i>In vivo:</i> 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).	<i>In vitro:</i> 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).	<i>In vivo:</i> 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).	<i>In vivo:</i> 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).	<i>In vivo:</i> Cat trachea.	Cigarette smoke.	<i>Percent decrease in ciliary activity</i> Control 0 Unfiltered smoke 53 Cellulose acetate filter 45 Carbon cellulose acetate filter 30
Dalhamn, 1966, Sweden (60).	<i>In vivo:</i> Cat trachea.	Cigarette smoke.	<i>Mean number of puffs required to produce ciliastasis</i> 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).	<i>In vivo:</i> 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).	<i>In vivo:</i> 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).	<i>In vivo:</i> 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).	<i>In vivo:</i> 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).	<i>In vivo:</i> Common mollusk ciliated epithelium.	Cigarette smoke dissolved in sea water.	Significant ciliastasis, reversible.
Battista and Kensler, 1970, U.S.A. (28).	<i>In vitro:</i> 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).	<i>In vivo:</i> 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).	<i>In vivo</i> : Cat trachea.	Unfiltered cigarette and cigar smoke.	Average number of puffs required to arrest ciliary activity Cigarette smoke 73 } (p<0.01) Cigar smoke 114 } 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).	<i>In vivo</i> : 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 ciliotoxic, 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.		<p style="text-align: center;"><i>Surface tension values of surfactant</i></p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th>20 percent area</th> <th>100 percent area</th> <th>Stability index (reflects surfactant activity)</th> <th>† Values significantly different from values of normals at p<0.02 level.</th> </tr> </thead> <tbody> <tr> <td>Normal</td> <td>6.5</td> <td>60.0</td> <td>1.61</td> <td></td> </tr> <tr> <td>Pulmonary patients</td> <td>†17.0</td> <td>†50.0</td> <td>1.00</td> <td></td> </tr> <tr> <td>Chronic smokers</td> <td>15.7</td> <td>51.0</td> <td>1.04</td> <td></td> </tr> </tbody> </table>		20 percent area	100 percent area	Stability index (reflects surfactant activity)	† Values significantly different from values of normals at p<0.02 level.	Normal	6.5	60.0	1.61		Pulmonary patients	†17.0	†50.0	1.00		Chronic smokers	15.7	51.0	1.04	
	20 percent area	100 percent area	Stability index (reflects surfactant activity)	† Values significantly different from values of normals at p<0.02 level.																			
Normal	6.5	60.0	1.61																				
Pulmonary patients	†17.0	†50.0	1.00																				
Chronic smokers	15.7	51.0	1.04																				
Giammona, 1967, U.S.A. (94)	<i>In vitro:</i> Surfactant material induced from dogs and rats. <i>In vivo:</i> Dogs, cats, and guinea pigs.	Exposed to cigarette smoke for 3 hours/day for up to 3 weeks.	<i>In vitro:</i> Exposure to cigarette smoke was associated with a significant decrease in maximal surface tension. <i>In vivo:</i> 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.	<p style="text-align: center;"><i>Surface tension values of surfactant</i></p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th>20 percent area</th> <th>100 percent area</th> <th>Stability index</th> </tr> </thead> <tbody> <tr> <td>Control</td> <td>11</td> <td>7.1</td> <td>1.60</td> </tr> <tr> <td>Smoke</td> <td>10</td> <td>18.7</td> <td>0.84</td> </tr> </tbody> </table> <p style="text-align: center;">(p<0.002) (p<0.002)</p>		20 percent area	100 percent area	Stability index	Control	11	7.1	1.60	Smoke	10	18.7	0.84								
	20 percent area	100 percent area	Stability index																				
Control	11	7.1	1.60																				
Smoke	10	18.7	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	
				Cases	Controls			
Mills, 1950, U.S.A. (167).	118 male and female patients with pneumonia and 472 healthy individuals from "random" sample.	Hospital Interview.	Mean age	49.6	49.6	The author stated that there was a significant difference in tobacco usage between the two groups.		
			NS	15.25	25.21			
			Cigarettes only	63.56	52.33			
			Mixed	21.19	22.46			
Lowe, 1956, England (157).	520 male and 185 female tuberculosis patients and 419 male and 249 female control outpatients.	Interview by trained social worker.	<i>Males</i>		<i>Females</i>		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	
			NS	2.5	8.1	Cases		Controls
			Cigarettes/day: 1-9	9.2	12.9	37.3		51.4
			10-19	38.1	35.6	20.5		25.7
			20-29	29.4	27.4	30.8		20.5
			30-39	11.3	9.3	11.4		2.4
			>40	9.4	6.7			
Dowling, et al., 1957, U.S.A. (72).	Individuals exposed to "infectious cold agent" and placebo.	Interview and medical examination.	<i>Exposed to placebo</i>		<i>Exposed to infectious agent</i>		No statistically significant differences noted.	
			<i>Percent developing "cold"</i>		<i>Percent developing "cold"</i>			
			NS	Number	Number	Number		
			111	10	328	34		
			SM	78	14	249	35	

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

(Actual number of cases shown in parentheses)

SM = Smokers NS = Nonsmokers

Author, year, country, reference	Number and type of population	Data collection	Results			Comments	
Boake, 1958, U.S.A. (33).	Parents of 59 families.	Interview		<i>Person-years</i>	<i>Number of respiratory illnesses person-years</i>	No statistically significant differences noted.	
			NS	120	624		5.2
			Cigarettes/day: 1-10	99	529		5.3
			11-20	108	486		4.5
			>20	99	424		4.3
Pipe, cigar	72	304	4.2				
Shah et al., 1959, India (205).	Tuberculosis institute employees.	Survey, X-ray, and interview.		<i>Tuberculous by X-ray</i>	<i>Normal or nontuberculous</i>	† 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	
			<i>Smoking habits prior to diagnosis</i>				
Brown et al., 1961, Australia (4).	306 male and female tuberculosis clinic patients, 221 male and female outpatients.	Interview	<i>Tuberculous patients (percent)</i>			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.	
			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					
Haynes et al., 1966, U.S.A. (108).	191 male prep school students.	Interview	<i>Average number of respiratory illnesses/10 students (adjusted for age)</i>				
				<i>All respiratory episodes</i>	<i>All severe respiratory episodes</i>		<i>All severe lower or combined respiratory episodes</i>
			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 and parents' occupational class.	Interview and health service records.	<i>Median number of illnesses/student</i>			The authors noted that these differences were statistically significant. † Particularly tracheitis, bronchitis, and pneumonia.	
				<i>All respiratory diseases†</i>	<i>All other illnesses</i>		
			NS (47)	2.08	2.99		
SM (47)	2.54	5.00					

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. (188).	1,496 Harvard and 370 Radcliffe students.	Medical history, chart review, and questionnaire.	<i>Number of visits to student health unit for respiratory illness/student (common colds, pharyngitis, bronchitis, laryngitis, pneumonia—not allergic rhinitis)</i>		† p<0.001.	
				<i>Harvard</i>		<i>Radcliffe</i>
			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					
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.	<p>Heavy smokers—21 percent more clinical illnesses than nonsmokers; 20 percent more requiring bed rest than nonsmokers</p> <p>Light smokers—10 percent more clinical illnesses than nonsmokers; 7 percent more requiring bed rest than nonsmokers.</p>	<p>The authors also noted that:</p> <p>(a) Smokers exhibited serologic evidence of increased subclinical A₂/HK/68 infection.</p> <p>(b) There was no difference in the vaccination status between smokers and nonsmokers.</p>		

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

Men over 20					
Group	Cases	Percent chest clear	Percent bronchitis	Percent broncho-pneumonia and atelectasis	Percent total complication rate
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

Arterial oxygen saturation (percentage)					
Group	Case number	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

Contents

	<i>Page</i>
Introduction	237
Lung Cancer	239
Epidemiological Studies	240
Prospective Studies	240
Retrospective Studies	240
Lung Cancer Trends in Other Countries	244
Histology of Lung Tumors	246
Lung Cancer Relationships in Women	251
Lung Cancer, the Urban Factor, and Air Pollution....	252
Lung Cancer and Occupational Hazards	256
Uranium Mining	256
Other Occupations.....	256
Nickel.....	256
Asbestos.....	257
Arsenic.....	257
Chromium.....	257
Pathological Studies.....	258
Pulmonary Carcinogenesis	258
General Aspects of Carcinogenesis	258
Polynuclear Aromatic Hydrocarbons	264
Nitrosamine Compounds.....	264
Pesticides and Fungicides.....	266
Radioactive Isotopes	266
Inhibitors of Ciliary Movement	267
Experimental Studies	267
Skin Painting and Subcutaneous Injection...	267
Tissue and Organ Culture	267
Tracheobronchial Implantation	
and Instillation	268
Inhalation	268
Reduction in Tumorigenicity	275
Summary and Conclusions	276
Cancer of the Larynx	277
Epidemiological Studies	277
Pathological Study	280
Experimental Study	281
Summary and Conclusions	281
Oral Cancer	284
Epidemiological Studies	285
Experimental Studies	288
Summary and Conclusions	289

	<i>Page</i>
Cancer of the Esophagus	289
Epidemiological Studies	289
Pathological Study	292
Experimental Studies	292
Summary and Conclusions	293
Cancer of the Urinary Bladder and Kidney	293
Epidemiological Studies (Bladder)	293
Epidemiological Studies (Kidney)	296
Experimental Studies	296
Summary and Conclusions	299
Cancer of the Pancreas	299
Summary and Conclusions	299
References	299

FIGURES

1. Lung cancer, Finland and Norway	245
2. Percent of smoking dogs with tumors	274
3. Percent of lung lobes with tumors in smoking dogs	274
4. Effects of chronic cigarette smoke inhalation on the hamster larynx	284

LIST OF TABLES

1. Lung cancer mortality ratios	241
2. Lung cancer mortality ratios for males by duration of cigarette smoking	244
A3. Outline of methods used in retrospective studies of smoking in relation to lung cancer	323
A4. Group characteristics in retrospective studies on lung cancer and tobacco use	329
5. Annual means of total lung cancer mortality and sex ratios for selected periods in Finland and Norway	246
6. Epidemiologic and pathologic investigations concern- ing smoking and histology of lung cancer	247
A7. Grouping of pulmonary carcinomas	334
8. Tumor prevalence among males and females 35-69 years of age, by type of tumor and smoking category	250
9. Epidemiologic investigations concerning the relation- ship of lung cancer to smoking, air pollution, and urban or rural residence	253
10. Pathologic and cytologic findings in the tracheo- bronchial tree of smokers and nonsmokers	259

LIST OF TABLES (Continued)

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

	<i>Page</i>
11. Identified or suspected tumorigenic agents in cigarette smoke	265
A12. Autopsy studies concerning the presence of radioactivity in the lungs of smokers	335
A13. Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals	337
A14. Experiments concerning the effect of cigarette smoke or its constituents on tissue and organ cultures ..	343
A15. Experiments concerning the effect of the instillation or implantation of cigarette smoke or its constituents into the tracheobronchial tree of animals	346
A16. Experiments concerning the effect of the inhalation of cigarette smoke or its constituents upon the respiratory tract of animals	349
17. Data on pedigreed male beagle dogs of groups F, L, H, h and N	270
18. Summary of principal cause of death (days No. 57 through No. 875) in dogs of groups F, L, H, h and N	271
19. Data on dogs with lung tumors indicating type of tumor and lobe in which the tumor was found	272
20. Laryngeal cancer mortality ratios—prospective studies	278
A21. Outline of retrospective studies of tobacco use and cancer of the larynx	354
A22. Summary of results of retrospective studies of tobacco use and cancer of the larynx	358
A23. Number and percent distribution by relative frequency of atypical nuclei among true vocal cord cells, of men classified by smoking category	359
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	360
25. Deposition of ¹⁴ C-labeled smoke particles in particular regions of the respiratory tract	282
26. Classification of the five registered stages of epithelial changes at the larynx	283
27. Oral cancer mortality ratios—prospective studies..	286
A28. Outline of retrospective studies of tobacco use and cancer of the oral cavity	361
A28a. Summary of results of retrospective studies of smoking by type and oral cancer of the detailed sites..	368

LIST OF TABLES (Continued)
 (A indicates tables located in appendix at end of chapter)

	<i>Page</i>
A29. Experimental studies concerning oral carcinogenesis	371
30. Esophageal cancer mortality ratios—prospective studies	290
A31. Summary of methods used in retrospective studies of tobacco use and cancer of the esophagus	375
A31a. Summary of results of retrospective studies of tobacco use and cancer of the esophagus	378
A32. Atypical nuclei in basal cells of epithelium of esophagus of males, by smoking habits and age	379
A33. Atypical nuclei in basal cells of epithelium of esophagus of males, by amount of smoking and age	380
34. Kidney and urinary bladder cancer—prospective studies	294
A35. Summary of methods used in retrospective studies of smoking and cancer of the bladder	381
A35a. Summary of results of retrospective studies of smoking and cancer of the bladder	383
36. Pancreatic cancer mortality ratios—prospective studies	298

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 pre-malignant 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		Pipe	No data	Bronchogenic (Excluding adenocarcinoma)	341/448			
				SM . 443	NS . 15					NS 1.00 (15)	SM 2.57 (18)	Never smoked 1.00
					<10 8.00 (24)	Cigar		Previously <1 pack/day	† With or without microscopic proof.			
					10-20 10.50 (84)			Continuing 16.94				
					>20 23.40 (117)	NS 1.00 (15)		Duration } <1 year . . . 16.50				
					All †10.73 (397)	SM 1.00 (7)		of } 1-10 years . . . 10.44				
								cessation } >10 years . . . 1.51				
								Previously >1 pack/day				
								Continuing 46.21				
								Duration } <1 year . . . 58.23				
								of } 1-10 years . . . 22.82				
								cessation } >10 years . . . 17.79				
Doll and Hill, 1964, Great Britain (74).	Approximately 41,000 male British physicians	Questionnaire and followup of death certificate.	10	212		Pipe and Cigar Grams/day	No data	Cigarette smokers	† Refers to current cigarette smokers only.			
				SM . 209	NS . 3					NS 1.00 (3)	NS 1.00 (3)	NS 1.00 (3)
										1-14 8.14 (22)		Continuing 18.29 (124)
										15-24 19.86 (53)		Duration } <5 years . . . 9.57 (5)
		>25 32.43 (57)		1-14 6.00 (12)		of } 5-9 years . . . 7.00 (7)						
						15-24 6.43 (6)		cessation } 10-20 years . . . 2.57 (3)				
						>25 13.71 (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		Pipe	No data	Ex-smokers of cigarettes only	† Refers to current cigarette smokers only.			
				†SM . 324	NS . 7					NS 1.00 (7)	NS 1.00 (7)	NS 1.00 (7)
										<10 10.00 (57)	SM 4.35 (18)	Ex-smokers of cigarettes only 6.06 (18)
										10-20 16.41 (204)		
		>20 17.31 (63)		Cigar								
		All 14.20 (245)		NS 1.00 (7)								
						SM 2.94 (2)						

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 person years.	Questionnaire and followup of death certificate.	8½	1,256	SM .1,178	NS 1.00 (78)	NS1.00 (78)	No data	NS 1.00 (78)			
					NS . 78	1-9 5.49 (45)	SM1.84 (17)					
						10-20 ... 9.91(303)	Cigar					
						21-39 ...17.41(315)	NS1.00 (78)					
						>39 ...23.93 (82)	SM1.59 (6)					
						All12.14(749)	Pipe and cigar					
							NS1.00 (78)					
							SM1.66 (20)					
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		Current cigarettes only		Pipe		Males		
					1,159		NS1.00 (49)	NS 1.00 (49)				
					SM .1,110		SM2.24 (21)	Slight 8.42(120)				
					NS . 49	NS 1.00 (49)		Cigar	Moderate ...11.45(311)			
						1-9 4.60 (26)	NS1.00 (49)	Deep14.31(141)				
						10-19 ... 7.48 (82)	SM1.85 (22)					
						20-39 ...13.14(381)	Pipe and cigar					
						>40 ...16.61 (82)	NS1.00 (49)					
						All 9.20(719)	SM0.90 (11)	Moderate } ... 3.70 (45)				
								Deep }				
				Females								
				NS 1.00(102)								
				1-19 1.06 (20)								
				>20 4.76 (50)								
				All 2.20 (81)								

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)				Preliminary report.
					1-24 2.69 (29)				
					>25 5.68 (5)				
Weir and Dunn, 1970, U.S.A. (506).	68,153 males in various occupations in California.	Questionnaire and followup of death certificate.	5-8	368	NS 1.00				NS include pipe and cigar smokers SM include ex-smokers.
					±10 3.72				
					±20 9.05				
					>30 9.56				
					All 7.61				

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	85-94
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-

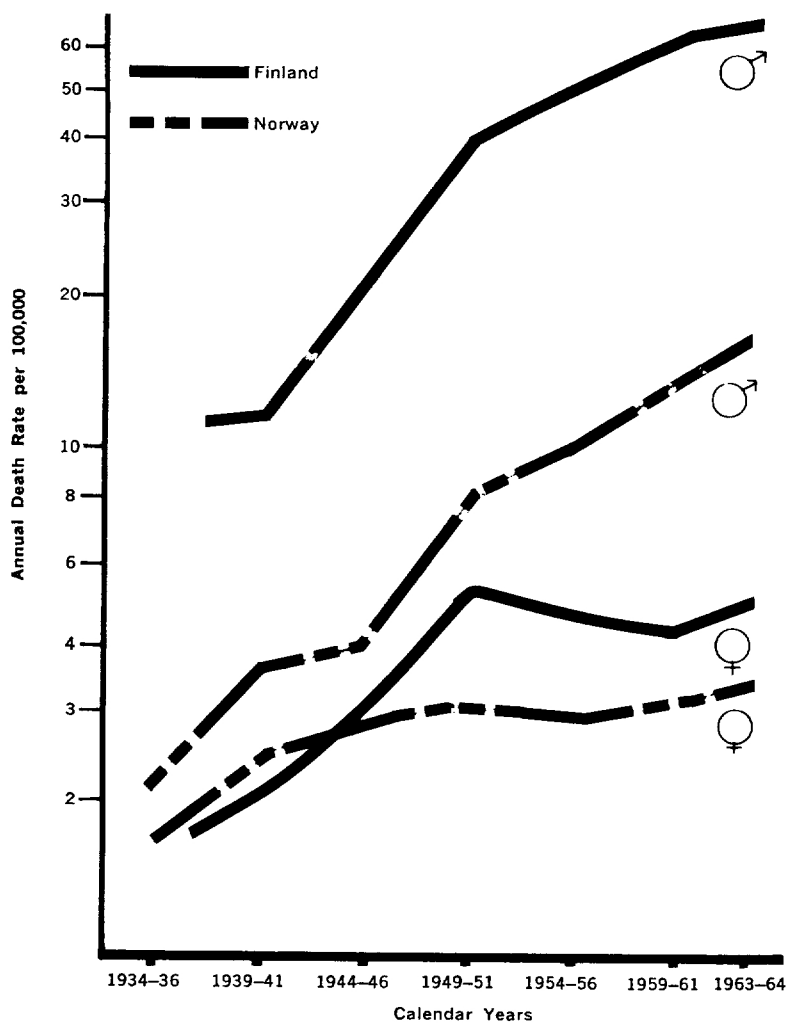


FIGURE 1.—Lung cancer, Finland and Norway.
SOURCE: Kreyberg, L. (154).

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 cancer¹
(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.	<i>Percent cases by histologic type and smoking history</i>			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.	
		<i>All lung cancers other than adenocarcinoma (605)</i>				
		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.	<i>Percent patients with lung cancer by average amount smoked daily over 10 years</i>			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.	
		<i>Males</i>				
			<i>Epidermoid (475)</i>	<i>Oat-cell or anaplastic (303)</i>		<i>Adenocarcinoma (33)</i>
		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)
		<i>Females</i>				
			<i>Epidermoid (18)</i>	<i>Oat-cell or anaplastic (38)</i>		<i>Adenocarcinoma (10)</i>
		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)			

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.	<i>Percent of patients with specific lung cancers by tobacco usage during the 20 years prior to study</i>				
		<i>All lung cancers other than adenocarcinoma</i>				
			<i>Adenocarcinoma</i>	<i>Controls</i>		
		Nonsmokers	5.9	13.0	24.4	
Cigarette smokers	94.1	87.0	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.	<i>Percent of smokers by histologic type and smoking history</i>				
			<i>Epidermoid</i>	<i>Anaplastic</i>	<i>Unknown type</i>	<i>Cylindrical</i>
		Cases	96.0	97.0	96.0	100.0
Controls	79.0†	83.0†	79.0†	96.0	† Difference significant at $p \leq 0.05$ level.	
Haenszel et al., 1958, U.S.A. (119).	158 female cases of lung cancer.	<i>Relative risk for specified tumors (smokers/nonsmokers)</i>			134 cases with final histological determination. † Difference from unity significant at $p \leq 0.01$.	
		Adjusted for age and occupation	<i>Group I (Kreyberg)</i>			<i>Adenocarcinoma</i>
Haenszel and Shimkin, 1962, U.S.A. (112).	2,191 male cases of lung cancer with adequate histologic data.	<i>Standardized mortality ratios</i>			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.	
		<i>Epidermoid and undifferentiated carcinomas</i>				<i>Adenocarcinoma</i>
		White males total	100			100
		Never smoked	6			18
		Ex-smokers	34			46
		<1 pack/day	123			116
>1 pack/day	499		467			

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.	<i>Percent cases by histologic type and smoking history (number of smokers)</i>				The authors also noted that: 1. Adenocarcinomas were 2 1/3 times more common in women 2. Only 1 percent of Kreyberg Group I cases were nonsmokers.	
			<i>Squamous</i>	<i>Undifferentiated</i>	<i>Adenocarcinoma</i>		<i>Alveolar</i>
		Nonsmokers	1.0 (3)	10.0 (17)	23.0 (8)		20.0 (1)
		Smokers	89.0 (183)	90.0 (145)	60.0 (20)		
Ashley and Davies, 1967, England (6).	442 male and female cases of histologically diagnosed lung cancer.	<i>Percent cases by histologic type and smoking history</i>				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.	
			<i>Undifferentiated</i>	<i>Squamous</i>	<i>Adenocarcinoma</i>		
		Nonsmokers	2.8 (4)	2.5 (6)	3.4 (2)		
		Pipe	9.9 (14)	9.9 (24)	1.7 (1)		
		Cigarette	87.3 (124)	87.6 (211)	94.9 (56)		
		<10/day	14.1 (20)	22.4 (54)	22.0 (13)		
		10-20	33.8 (48)	41.5 (100)	33.9 (20)		
		21-30	12.0 (17)	21.6 (52)	16.9 (10)		
31-40	14.1 (20)	12.9 (31)	8.5 (5)				
>40	7.1 (10)	6.2 (15)	5.1 (3)				
Ormos et al., 1969, Hungary (204).	118 male and female cases of histologically proven lung cancer with adequate smoking information.	<i>Percent cases by histologic type and smoking history</i>				The author noted that the small number of cases allows for no definite conclusions.	
			<i>Group I</i>	<i>Group II and large cell carcinomas</i>			
		Nonsmokers	21.0 (18)	36.0 (9)			
	Smokers	79.0 (68)	64.0 (16)				

¹ Data obtained from patient interview and other sources.

TABLE 8.—Tumor prevalence among males and females 35–69 years of age, by type of tumor and smoking category
(Smokers constituted 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
Bronchiol-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
Bronchiol-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 non-smokers 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.	<i>Lung cancer mortality (1950) per 1,000</i>									
		Age:	<i>Males</i>			<i>Females</i>			<i>Nonsmokers</i>		
			<i>London</i>	<i>Other urban</i>	<i>Rural</i>	<i>London</i>	<i>Other urban</i>	<i>Rural</i>	<i>All areas</i>		
			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	0.219				
Stocks and Campbell, 1955, England (265).	Death rates in England and Northern Wales. Review of patient chart or interview with kin or physicians.	<i>Male lung cancer death rates 1952-54 (per 100,000) ages 54-74</i>									
		Nonsmokers	<i>Rural (68)</i>			<i>Mixed (118)</i>			<i>Urban (539)</i>		
			Pipe	14			..			131	
			Cigarettes: Light	41			25			143	
			Moderate	87			153			297	
			Heavy	183			132			287	
	363			303			394				
Hammond and Horn, 1958, U.S.A. (120).	187,783 white males in 9 states. Questionnaire and interview.	<i>Age standardized death rates due to bronchogenic carcinoma (males)</i>									
		Nonsmokers	<i>Rural</i>	<i>Suburb or town</i>	<i>City of 10,000-50,000</i>	<i>City of >50,000</i>					
			..	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	
Buell et al., 1967, U.S.A. (49).	304 lung cancer deaths among American Legionnaires aged 25 and over. Questionnaires to next of kin.	<i>Age-adjusted lung cancer death rates per 100,000 man years and mortality ratios</i>						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.	
		<i>Los Angeles</i>		<i>San Francisco/San Diego</i>		<i>All other California counties</i>			
			<i>Rate</i>	<i>Ratio</i>	<i>Rate</i>	<i>Ratio</i>	<i>Rate</i>		<i>Ratio</i>
		Nonsmokers	28.1	2.5	43.9	3.9	11.2		1.0
		Smokers:							
		<1 pack/day	63.6	5.7	77.1	6.9	61.02		5.4
		>1	241.3	21.5	226.0	20.2	137.5		12.3
Hitosugi, 1968, Japan (126).	185 male and female lung cancer deaths and 4,191 matched controls aged 35-74. Data from questionnaires and interviews.	<i>Lung cancer death rate per 100,000</i>						The authors postulated a slight synergistic effect between smoking and air pollution.	
			<i>Pollution region</i>						
			<i>Low</i>	<i>Intermediate</i>	<i>High</i>				
		<i>Males</i>							
		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				
		<i>Females</i>							
		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						
	<i>Age- and smoking-adjusted lung cancer death rate per 100,000</i>								
		<i>Low</i>	<i>Intermediate</i>	<i>High</i>					
<i>Males</i>	16.1	22.4	28.4						
<i>Females</i>	7.5	11.6	8.7						

LUNG CANCER AND OCCUPATIONAL HAZARDS

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 intratracheal 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.	<i>Percent of cases with bronchial basal cell hyperactivity</i>					Smokers included pipe and cigar smokers. † $p \leq 0.01$ in comparison with nonsmokers.	
		Nonsmokers				23.5 (34)		
		Smokers				43.7 (71)		
		Heavy smokers				†61.3 (31)		
Hamilton et al., 1957, U.S.A. (117).	Selected autopsy material.	<i>Percent of cases with:</i>					No lung cancer patients included.	
			<i>Number</i>	<i>Age range</i>	<i>Basal cell hyperplasia</i>	<i>Squamous metaplasia</i>		<i>Transitional metaplasia</i>
		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.	<i>Percent of cases with bronchial squamous epithelial metaplasia</i>					Nonsmokers include those smoking less than or equal to 5 grams per day.	
		Nonsmokers				54.0 (39)		
		Pipe				80.5 (20)		
		All cigarette				79.0 (38)		
		Cigarettes per day:						
		5-14				70.0 (23)		
15-25				90.0 (10)				
>25				100.0 (5)				
Knutson, 1960, U.S.A. (147).	100 persons 23-85 years of age autopsied at Seattle Veterans Hospital on whom smoking data was available.	<i>Percent of cases with:</i>					Age, occupation, and site of residence were found to have no appreciable effect.	
			<i>No. of Persons</i>	<i>No change</i>	<i>Basal cell hyperplasia</i>	<i>Squamous metaplasia</i>		<i>Atypical proliferative metaplasia</i>
		Nonsmokers	(21)	47.6	28.6	14.3		9.5
		Cigarettes/day:						
		1-9	(9)	77.8	11.1	11.1		..
		10-15	(11)	18.2	18.2	54.5		9.1
		16-20	(44)	20.4	29.5	29.5		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 re- lation of smoking to: a. loss of cilia, b. increase in number of atypical cells, c. carcinoma <i>in situ</i> . 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				
Cross et al., 1961, U.S.A. (64).	140 persons autopsied at Iowa City Veterans Hospital on whom smoking data was available.	Percent sections showing changes in bronchial epithelium (number of sections) †						
			Normal	Hyperplasia	Squamous metaplasia	Atypical metaplasia	Carcinoma <i>in situ</i>	Carcinoma
		Nonsmokers (31)	61 (562)	36 (137)	8 (33)	†15 (58)
Smokers (109)	44 (570)	43 (562)	16 (197)	20 (263)	1 (12)	2.6 (34)		
							† The authors noted that the differ- ence between smokers and non- smokers was statistically significant.	

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	
			<i>Number of sections of bronchial epithelium</i>	<i>Percent sections with cilia absent and entirely atypical cells</i>	<i>Percent sections with some atypi- cal cells and cilia absent</i>	<i>Percent sections with 50 percent atypical cells and cilia present</i>		
Auerbach et al., 1962, U.S.A. (14).	72 autopsied former ciga- rette smokers who had been smoking for ≥10 years and had ceased ≥5 years ago.	<i>Number</i>					Each ex-smoker matched with a current smoker plus never-smoker for age, occupa- tion, and resi- dence. There was an average of 50.3 sections per subject and none had less than 18 sections.	
		Nonsmokers	72	3,156	0.0	0.1		0.5
		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 sec- tions with cilia absent and entirely atypical cells	Percent sec- tions with some atypi- cal cells and cilia absent	Percent sec- tions 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, occu- pation, and residence.	Males:					Major findings noted: Urban nonsmokers showed more lesion than rural. Both lesions and atypical nuclei were much less frequent in non- smokers 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.	<i>Percent in each cytologic class</i>					Smokers defined as those having con- sumed ≥ 10 ciga- rettes a day for ≥ 1 year.	
			<i>Normal</i>	<i>Slightly atypical</i>	<i>Moderately atypical</i>	<i>Strongly atypical</i>		
		Nonsmokers (45)	86.7	4.4	8.9	..		
Smokers (58)	55.2	32.8	10.8	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		
			Number	Percent showing metaplasia				
Maltoni et al., 1968, Italy (182).	1,000 healthy males who underwent sputum induction.	Nonsmokers	294	41.16				
		Smokers:						
		1-10 cigarettes/day	189	47.09				
		11-20	385	51.43				
		21-30	93	61.29				
		>30	39	69.28				
Nasiell, 1968, Sweden (198).	50 nonsmoking outpatients, 398 smokers participating in general health examination who underwent sputum induction.	<i>Sputum cytologic changes</i>				† Regarded by author as "real premalignant change."		
			<i>Number</i>	<i>Percent Males</i>	<i>Mean age</i>		<i>Percent with metaplasia</i>	<i>Percent with atypical metaplasia†</i>
		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).	<i>Males:</i>				The authors found no evidence of carcinoma <i>in situ</i> or preneoplastic atypical changes.		
			<i>Number</i>	<i>Percent with metaplasia</i>				
		Nonsmokers	36	50.0				
		Ex-smokers	21	57.7				
		<1 pack	32	62.5				
		>1 pack	68	73.5				
		<i>Females:</i>						
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-butyl nitrosamine	Trace	
4. Nitrosopyrrolidine	0.4	
5. Nitrosopiperidine	Trace	
Epoxides, peroxy compounds, and lactones:		
1. Epoxides	No data	Certain of these compounds are known carcinogens; presence in smoke condensate not established.
2. Peroxides	Present	
3. Lactones	
a. α -Levantenolide	20.0	
b. β -Levantenolide	2.0	
N-alkyl-heterocyclics:		
1. 1-methylindole	Present	Possible initiator.
Pesticides and fungicides: ⁴		No essential contribution suspected.
1. TDE	10-100	
2. o,p'-DDD	10-100	
3. DDT	10-100	
4. Maleic hydrazide	10-100	
Beta-naphthylamine	2-3	Suspected bladder carcinogen; of doubtful significance at reported levels.
Polonium 210	1-50 picocuries	Of some importance only in the case of relatively high concentration, but not important at reported levels.
Nickel compounds	Present	Suspected carcinogens of some importance.

TABLE 11.—Identified or suspected tumorigenic agents in cigarette smoke¹
(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 tumorigenicity 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 H³-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		Early squamous cell bronchial carcinoma
				Non-invasive	Invasive	
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	—	—
Group H (no filter)	L 899a	3,195	5.4	LA	—	—
	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		Early squamous cell bronchial carcinoma	
				Non-invasive	Invasive		
Group h (no filter)	h	606	4.6	LA	—	—	
	h	626	4.4	..	I.A, RI	—	
	h	649	4.143	5.0	RI	I.A, 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).

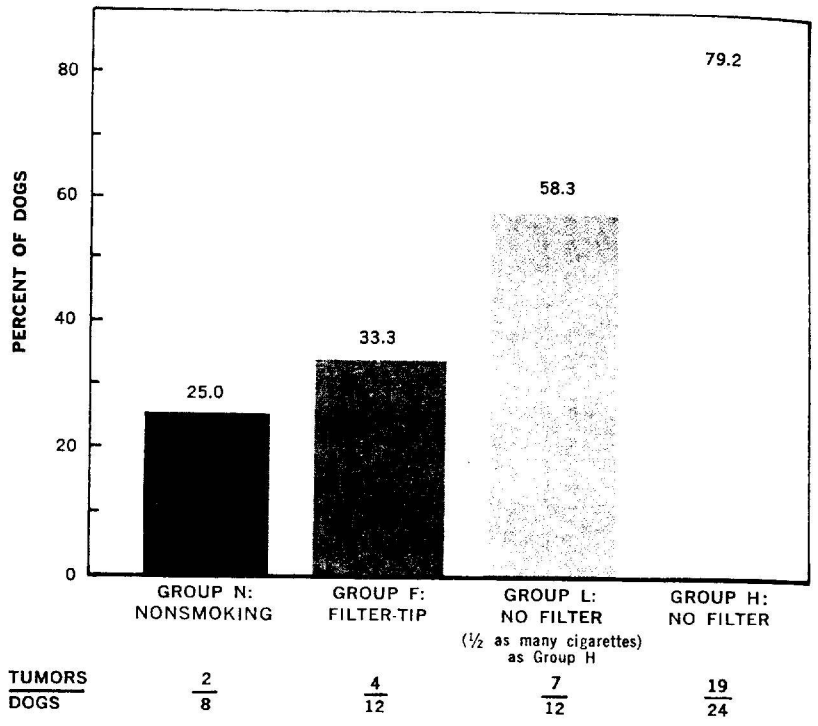


FIGURE 2.—Percent of smoking dogs with tumors.
SOURCE: Adapted from Auerbach, O., et al. (11).

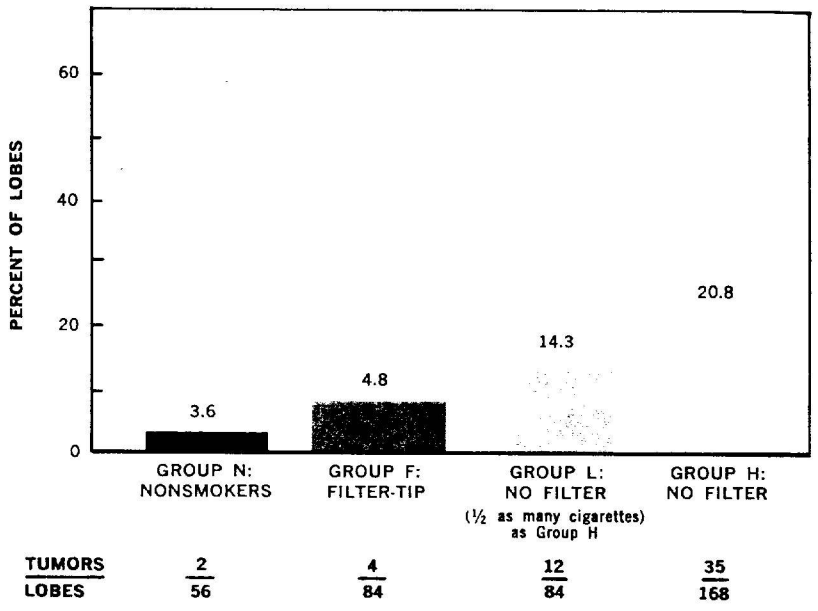


FIGURE 3.—Percent of lung lobes with tumors in smoking dogs.
SOURCE: Adapted from Auerbach, O., et al. (11).

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 non-smokers. 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, 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 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 laryngeotracheal 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	NS	—	No nonsmokers died of laryngeal carcinoma, therefore ± 10 smoker set as 1.00 standard. NS includes pipe and cigar smokers. SM includes ex-smokers.
				..11	± 10	1.00	
				.. 0	± 20	5.99	
					>30	5.84	

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

the hypopharynx. These authors noted that the percentage of heavy smokers among the patients with cancer of both the extrinsic and intrinsic larynx was significantly greater than that among controls. However, it is of interest that the excess risk of laryngeal cancer among cigar and pipe smokers in this study could be attributed to the extrinsic laryngeal group.

As in studies of oral cancer, it appears that alcohol consumption should also be taken into account in studies of laryngeal cancer. Wynder, et al. (312) reported a significantly increased risk of extrinsic cancer among those with alcohol intake above 7 ounces of whiskey per day. With less than this amount, no increased risk was evident. Schwartz, et al. (248), noted no effect in relation to alcohol intake. Further research into the interaction of these two variables is necessary.

PATHOLOGICAL STUDY

Auerbach, et al. (9) studied histological changes in the larynges of 942 men, age 21 to 95, who were autopsied at a single hospital between 1964 and 1967. Cases of primary cancer of the larynx were excluded from the study. Smoking histories for all cases were obtained from family members of the deceased by trained interviewers. The randomized histological sections were graded by one observer. Tables A23 and A24 summarize the findings in the true vocal cord. Of the men who never smoked, 75 percent had no cells with atypical nuclei, only 4.5 percent had sections with areas containing 60 to 69 percent of cells with atypical nuclei, and none had a higher percentage. The 116 ex-smokers had laryngeal histology similar to that of the nonsmokers, as far as atypical nuclei were concerned. However, disintegrating nuclei were found in 40.5 percent of the ex-cigarette smokers and in only 0.4 percent of the remaining cases. Only one of the 91 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 ¹⁴C-labeled smoke particles in particular regions of the respiratory tract¹

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		7.6 (traced)	51.7	0.1-0.3	X561-187
Trachea	0.26				0.6	X62.3
Lungs	6.95				1000	X1
Total	14.12		² 14.7	100.0		

¹ Cigarettes labeled with ¹⁴C-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 Döntenwill, W. (76).

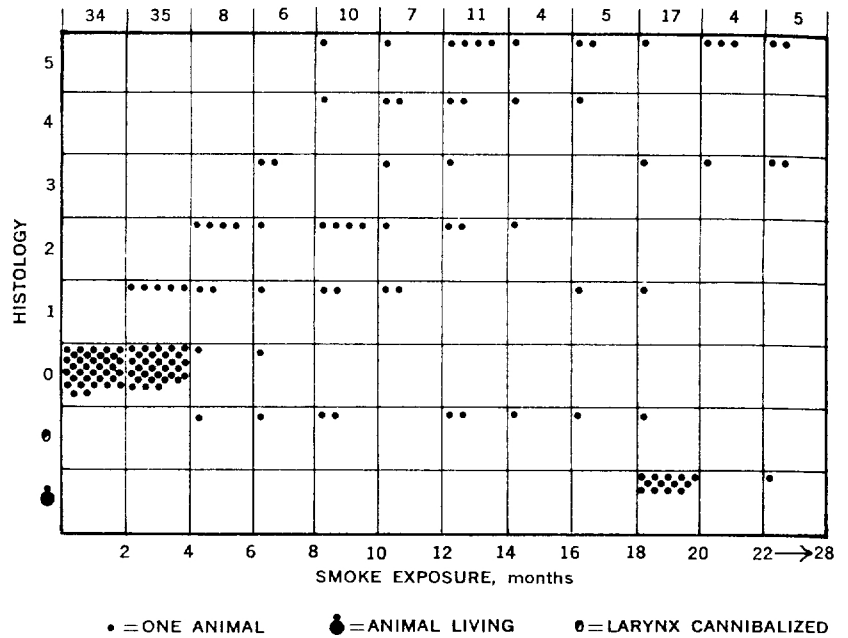


FIGURE 4.—Effects of chronic cigarette smoke inhalation on the hamster larynx. Review of the results of the inhalation experiments: number of smoke-exposed animals with and without changes in the larynx, duration of smoke exposure, and number of animals still alive. SOURCE: Dontenwill, W. (76).

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 oropharynx. 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 5/56 Mixed 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 — 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 502,971 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.	<i>Pipe</i> 2/33 <i>Mixed cigarette smokers</i> 2/33 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	<i>All smokers by amount in grams</i> NS 1.00 1-14 2.00 15-24 3.50 >25 5.00 All 3.00	† <i>Pipe and cigar</i> 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)	<i>Pipe</i> 1.99 (3) <i>Cigar</i> 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)	<i>Pipe and Cigar</i> 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 inter- view 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	NS includes pipe and cigar smokers.
					±20 1.69	>30 1.82	
					All 1.82		

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 that 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 (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	<i>Bladder</i> 224			NS	1.00 (39)	1.00 (52)	Bladder includes other urinary tract cancers.	
							Pipe	1.32 (6)	1.20 (8)		
							Cigar	0.77 (6)	0.94 (10)		
							Cigarettes/day:				
							1-9	0.97 (4)	1.10 (6)		
							10-19	1.34 (21)	1.93 (37)		
							20-39	1.68 (16)	3.20 (34)		
							>39	2.75 (5)	2.52 (5)		
	All	1.45 (46)	2.15 (82)								
Hirayama, 1967, Japan (135).	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			Bladder cancer only. Refers to all forms of smoking.		
					SM	10.00 (6)					
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	<i>Bladder</i> 27			NS	1.00	NS	1.00	SM include ex-smokers. NS include pipe and cigar smokers.
							±10	0.86	±10	1.52	
							±20	3.30	±20	2.81	
							>30	2.57	>30	5.41	
							All	2.46	All	2.89	

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^{-6} 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 acetylky-nurenine 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 acetylky-nurenine, 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	<i>Current (cigarettes only)</i>		<i>Pipes</i> NS ... 1.00 SM ... 2.60 (6) <i>Cigars</i> NS ... 1.00 SM ... 2.63 (1)	
					NS	1.00		
					<10	1.40 (5)		
					10-20	1.96 (16)		
					>20	2.37 (7)		
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)	Male data only.	
					SM (age			
					45-64)	2.69 (158)		
					SM (age			
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)	† Refers to current smokers of all types.	
					<i>Pipes</i>			
					NS	1.00 (88)		
					SM	0.74 (8)		
					<i>Cigars</i>			
					NS	1.00 (88)		
All	1.84 (125)							
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	} (p<0.01)	
					SM			
					15.56	(14)		
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	SM ... 71	NS	1.00	SM includes ex-smokers. NS includes pipe and cigar smokers.	
					±10	2.94		
					±20	2.45		
					>30	1.44		
					All	2.43		

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 ...

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.

REFERENCES

- (1) ABELIN, T., GSELL, O. T. Relative risk of pulmonary cancer in cigar and pipe smokers. *Cancer* 20(8) : 1288-1296, August 1967.
- (2) ALIFANO, A., PAPA, S., TANCREDI, F., ELICIO, M. A., QUA LIARIELLO, E. Tryptophan-nicotinic acid metabolism in patients with tumours of the bladder and kidney. *British Journal of Cancer* 18: 386-389, 1964.
- (3) ANTHONY, H. M., THOMAS, G. M. Bladder tumours and smoking. *International Journal of Cancer* 5(2) : 266-272, March 15, 1970.
- (4) ARKIN, A., WAGNER, D. H. Primary carcinoma of the lung. A diagnostic study of one hundred and thirty-five cases in 4 years. *Journal of the American Medical Association* 106(8) : 587-591, February 22, 1936.

- (5) ASH, J. E., BECK, M. R., WILKES, J. D. Tumors of the upper respiratory tract and ear. IN: Atlas of Tumor Pathology. Section IV—Fascicles 12 and 13. Washington, Armed Forces Institute of Pathology, 1964.
- (6) ASHLEY, D. J. B., DAVIES, H. D. Cancer of the lung. Histology and biological behavior. *Cancer* 20(2) : 165-174, February 1967.
- (7) AUERBACH, O. The pathology of carcinoma of the bronchus. *New York State Journal of Medicine* 49: 900-907, April 15, 1949.
- (8) AUERBACH, O., GERE, J. B., PAWLOWSKI, J. M., MUEHSAM, G. E., SMOLIN, H. J., STOUT, A. P. Carcinoma-*in-situ* and early invasive carcinoma occurring in the tracheobronchial trees in cases of bronchial carcinoma. *Journal of Thoracic Surgery* 34(3) : 298-309, September 1957.
- (9) AUERBACH, O., HAMMOND, E. C., GARFINKEL, L. Histologic changes in the larynx in relation to smoking habits. *Cancer* 25(1) : 92-104, January 1970.
- (10) AUERBACH, O., HAMMOND, E. C., KIRMAN, D., GARFINKEL, L., STOUT, A. P. Histologic changes in bronchial tubes of cigarette-smoking dogs. *Cancer* 20(12) : 2055-2066, December 1967.
- (11) AUERBACH, O., HAMMOND, E. C., KIRMAN, D., GARFINKEL, L. Effects of cigarette smoking on dogs. II. Pulmonary neoplasms. *Archives of Environmental Health* 21(6) : 754-768, December 1970.
- (12) AUERBACH, O., STOUT, A. P., HAMMOND, E. C., GARFINKEL, L. Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer. *New England Journal of Medicine* 265(6) : 253-267, August 10, 1961.
- (13) AUERBACH, O., STOUT, A. P., HAMMOND, E. C., GARFINKEL, L. Changes in bronchial epithelium in relation to sex, age, residence, smoking and pneumonia. *New England Journal of Medicine* 267(3) : 111-119, July 19, 1962.
- (14) AUERBACH, O., STOUT, A. P., HAMMOND, E. C., GARFINKEL, L. Bronchial epithelium in former smokers. *New England Journal of Medicine* 267(3) : 119-125, July 19, 1962.
- (15) AUERBACH, O., STOUT, A. P., HAMMOND, E. C., GARFINKEL, L. Histologic changes in esophagus in relation to smoking habits. *Archives of Environmental Health* 11(1) : 4-15, July 1965.
- (16) AWA, A., OHNUKI, Y., POMERAT, C. M. Some comparative effects of smoked paper, tobacco and cigarettes on chromosomes *in vitro*. *Texas Reports on Biology and Medicine* 19: 518-528, 1961.
- (17) BAIR, W. J. Inhalation of radionuclides and carcinogenesis. IN: Hanna, M. G., JR., Nettesheim, P., Gilbert, J.R. (Editors). *Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969.* U.S. Atomic Energy Commission Symposium Series 18, April 1970, pp. 77-101.
- (18) BENNINGTON, J. L., FERGUSON, B. R., CAMPBELL, P. B. Epidemiologic studies of carcinoma of the kidney. II. Association of renal adenoma with smoking. *Cancer* 22(4) : 821-823, October 1968.
- (19) BENNINGTON, J. L., LAUBSCHER, F. A. Epidemiologic studies on carcinoma of the kidney. I. Association of renal adenocarcinoma with smoking. *Cancer* 21(6) : 1069-1071, June 1968.
- (20) BERWALD, Y., SACHS, L. *In vitro* transformation of normal cells to tumor cells by carcinogenic hydrocarbons. *Journal of the National Cancer Institute* 34(4) : 641-658, October 1965.
- (21) BEST, E. W. R. A Canadian Study of Smoking and Health. Ottawa, Department of National Health and Welfare, 1966, 137 pp.

- (22) BIDSTRUP, P. L., CASE, R. A. M. Carcinoma of the lung in workmen in the bichromates-producing industry in Great Britain. *British Journal of Industrial Medicine* 13: 260-264, 1956.
- (23) BLACK, H., ACKERMAN, L. V. The importance of epidermoid carcinoma *in situ* in the histogenesis of carcinoma of the lung. *Annals of Surgery* 136(1): 44-55, July 1952.
- (24) BLACKLOCK, J. W. S. The production of lung tumours in rats by 3:4 benzpyrene, methylcholanthrene and the condensate from cigarette smoke. *British Journal of Cancer* 11(2): 181-191, 1957.
- (25) BLACKLOCK, J. W. S. An experimental study of the pathological effects of cigarette condensate in the lungs with special reference to carcinogenesis. *British Journal of Cancer* 15(4): 745-762, December 1961.
- (26) BLUMLEIN, H. Zur kausalen Pathogenese des Larynxkarzinoms unter Berücksichtigung des Tabakrauchens. (Causal pathogenesis of laryngeal carcinoma with respect to tobacco smoking.) *Archiv für Hygiene und Bakteriologie München* 139: 349-404, 1955.
- (27) BOCK, F. G. The nature of tumor-promoting agents in tobacco products. *Cancer Research* 28(11): 2363-2368, November 1968.
- (28) BOCK, F. G., MOORE, G. E. Carcinogenic activity of cigarette-smoke condensate. I. Effect of trauma and remote X irradiation. *Journal of the National Cancer Institute* 22(2): 401-411, February 1959.
- (29) BOCK, F. G., MOORE, G. E., CLARK, P. C. Carcinogenic activity of cigarette smoke condensates. III. Biological activity of refined tar from several types of cigarettes. *Journal of the National Cancer Institute* 34(4): 481-493, April 1965.
- (30) BOCK, F. G., MOORE, G. E., CROUCH, S. K. Tumor-producing activity of extracts of unburned tobacco. *Science* 145(3684): 831-833, August 21, 1964.
- (31) BOCK, F. G., MOORE, G. E., DOWD, J. E., CLARK, P. C. Carcinogenic activity of cigarette smoke condensate. Biological activity of refined tar from certain brands of cigarettes. *Journal of the American Medical Association* 181(8): 668-673, August 25, 1962.
- (32) BOREN, H. G. Pulmonary cell kinetics after exposure to cigarette smoke. IN: Hanna, M. G., JR., Nettlesheim, P., Gilbert, J. R. (Editors). *Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. U.S. Atomic Energy Commission Symposium Series 18, April 1970. pp. 229-241.*
- (33) BORENFREUND, E., KRIM, M., SANDERS, F. K., STERNBERG, S. S., BENDICH, A. Malignant conversion of cells *in vitro* by carcinogens and viruses. *Proceedings of the National Academy of Sciences of the United States of America* 56: 672-679, 1966.
- (34) BORISYUK, Y. P. Rak legkikh u krys, vyzvannyi intratrakheal'nym vvedeniyem produktov kureniya. (Cancer of the lung in rats induced by intratracheal intubation of tobacco smoke products.) *Voprosy Onkologii* 15(6): 49-53, June 1969.
- (35) BOUCHARD, J., MAY, R. M. L'effet des goudrons de tabac sur les greffes sous-capsulaires de poumon chez la souris. (The effect of tobacco tars on sub-capsular implants of the lung in mice.) *Archives d'Anatomie Microscopique et de Morphologie Experimentale* 49(3): 307-332, 1960.

- (36) BOYLAND, E. The Biochemistry of Bladder Cancer. Springfield C. C. Thomas, 1963. 95 pp.
- (37) BOYLAND, E., BUSBY, E. R., DUKES, C. E., GROVER, P. L., MANS Further experiments on implantation of materials into the u bladder of mice. *British Journal of Cancer* 18(3) : 575-581, Sep: 1964.
- (38) BOYLAND, E., ROE, F. J. C. Carcinogenic nitrosamines which n present in cigarette smoke. IN: Severi, L. (Editor). Lung Tum Animals. Perugia, Division of Cancer Research, University of Pe June 1966. pp. 667-676.
- (39) BOYLAND, E., WATSON, G. 3-hydroxyanthranilic acid, a carcinoge duced by endogenous metabolism. *Nature* 177(4514) : 837-838 5, 1956.
- (40) BOYLAND, E., WILLIAMS, D. C. The metabolism of tryptophan. : metabolism of tryptophan in patients suffering from the cancer bladder. *Biochemical Journal* 64 : 578-582, 1956.
- (41) BRADSHAW, E., SCHONLAND, M. Oesophageal and lung cancer in African males in relation to certain socio-economic factors. An ysis of 484 interviews. *British Journal of Cancer* 23(2) : 27. June 1969.
- (42) BRESLOW, L., HOAGLIN, L., RASMUSSEN, G., ABRAMS, H. K. Occup: and cigarette smoking as factors in lung cancer. *American Jour Public Health and the Nation's Health* 44(2) : 171-181, February
- (43) BRODERS, A. C. Squamous-cell epithelioma of the lip. A study o hundred and thirty-seven cases. *Journal of the American M Association* 74(10) : 656-664, March 6, 1920.
- (44) BROSS, I. D. J. Effect of filter cigarettes on the risk of lung cancer Wynder, E. L., Hoffmann, D. (Editors). *Toward a Less Ha Cigarette*. Bethesda, Md., U.S. Public Health Service, National C Institute Monograph No. 28, June 1968. pp. 35-40.
- (45) BROWN, R. R., PRICE, J. M., BURNEY, S. W., FRIEDEL, G. H. La effect of smoking on the excretion of tryptophan metabolites by *Cancer Research* 30(3) : 611-614, March 1970.
- (46) BROWN, R.R., PRICE, J. M., SATTER, E. J., WEAR, J. B. The metaboli: tryptophan in patients with bladder cancer. *Acta Unio Internatio Contra Cancrum* 16 : 299-303, 1960.
- (47) BRYAN, G. T. Rolē of tryptophan metabolites in urinary bladder ca *American Industrial Hygiene Association Journal* 30(1) : 2 January-February 1969.
- (48) BRYAN, G. T., BROWN, R. R., PRICE, J. M. Mouse bladder carcinogen of certain tryptophan metabolites and other aromatic nitrogen pounds suspended in cholesterol. *Cancer Research* 24(4) : 596-May 1964.
- (49) BUELL, P. E., DUNN, J. E., BRESLOW, L. Cancer of the lung and Angeles-type air pollution. Prospective study. *Cancer* 20(12) : 2 2147, December 1967.
- (50) CAHAN, W. G., KIRMAN, D. An effective system and procedure cigarette smoking by dogs. *Journal of Surgical Research* 8(12) : 575, December 1968.
- (51) CARNES, W. H. The respiratory epithelium of patients with lung can IN: *The Morphological Precursors of Cancer*. Proceedings of International Conference held at the University of Perugia, June 1

A publication of the Division of Cancer Research, University of Perugia, Italy. pp. 625-634.

- (52) CARUGNO, N., ROSSI, S. Evaluation of polynuclear hydrocarbons in cigarette smoke by glass capillary columns. *Journal of Gas Chromatography* 5(2) : 103-106, February 1967.
- (53) CASTIGLIANO, S. G. Influence of continued smoking on the incidence of second primary cancers involving mouth, pharynx, and larynx. *Journal of the American Dental Association* 77(3) : 580-585, September 1968.
- (54) CHAN, P. C., SANDERS, F. K., WYNDER, E. L. Effect of 3,4-benzo(a) pyrene on mouse lung primordia *in vitro*. *Nature* 228(5208) : 847-848, August 23, 1969.
- (55) CHANG, S. C. Microscopic properties of whole mounts and sections of human bronchial epithelium of smokers and non-smokers. *Cancer* 10(6) : 1246-1261, December 1957.
- (56) CLAPP, N. K., CRAIG, A. W. Carcinogenic effects of diethylnitrosamine in RF mice. *Journal of the National Cancer Institute* 39(5) : 903-916, November 1967.
- (57) COBB, B. G., ANSELI, J. S. Cigarette smoking and cancer of the bladder. *Journal of the American Medical Association* 193(5) : 329-332, August 2, 1965.
- (58) COHEN, S., HOSSAIN, S. Primary carcinoma of the lung. A review of 417 histologically proved cases. *Diseases of the Chest* 49(1) : 67-74, January 1966.
- (59) CONZELMAN, G. M., JR., MOULTON, J. E., FLANDERS, L. E., III, SPRINGER, K., CROUT, D. W. Induction of transitional cell carcinomas of the urinary bladder in monkeys fed 2-naphthylamine. *Journal of the National Cancer Institute* 42(5) : 825-836, May 1969.
- (60) COOK, J. W. Tobacco Smoke and Lung Cancer. London, The Royal Institute of Chemistry, Lecture Series No. 5, 1961. 18 pp.
- (61) CORNFIELD, J. A method of estimating comparative rates from clinical data. Applications to cancer of the lung, breast, and cervix. *Journal of the National Cancer Institute* 11 : 1269-1275, 1951.
- (62) CROCKER, T. T. Effect of benzo(a)pyrene on hamster, rat, dog, and monkey respiratory epithelia in organ culture. IN: Hanna, M. G., JR., Nettesheim, P., Gilbert, J. R. (Editors). *Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. U.S. Atomic Energy Commission Symposium Series 18, April 1970. pp. 433-443.*
- (63) CROCKER, T. T., NIELSEN, B. I., LASNITZKI, I. Carcinogenic hydrocarbons. Effects on suckling rat trachea in organ culture. *Archives of Environmental Health* 10(2) : 240-250, February 1965.
- (64) CROSS, K. R., WALZ, D. V., PALMER, G. K., WARNER, E. D. A study of the tracheobronchial epithelium and changes related to smoking. *Journal of the Iowa Medical Society* 51(3) : 137-140, March 1961.
- (65) DAVIES, R. F., DAY, T. D. A study of the comparative carcinogenicity of cigarette and cigar smoke condensate on mouse skin. *British Journal of Cancer* 23(2) : 363-368, June 1969.
- (66) DEELEY, T. J., COHEN, S. L. The relationship between cancer of the bladder and smoking. IN: *Bladder Cancer. Chapter 13, Proceedings of the 5th Inter-American Conference on Toxicology and occupational medicine, the University of Miami, School of Medicine, Coral Gables, Fla., 1966. pp. 163-169.*

- (67) DELLA PORTA, G., KOLB, L., SHUBIK, P. Induction of tracheobronchial carcinomas in the Syrian golden hamster. *Cancer Research* 18: 592-597, June 1958.
- (68) DIAMOND, L. The effect of carcinogenic hydrocarbons on rodent and primate cells *in vitro*. *Journal of Cellular and Comparative Physiology* 66: 183-195, 1965.
- (69) DOLL, R. Cancer of the lung and nose in nickel workers. *British Journal of Industrial Medicine* 15(4): 217-223, October 1958.
- (70) DOLL, R. Mortality from lung cancer among nonsmokers. *British Journal of Cancer* 7: 303-312, 1953.
- (71) DOLL, R. Mortality from lung cancer in asbestos workers. *British Journal of Industrial Medicine* 12(1): 81-86, January 1955.
- (72) DOLL, R. Occupational lung cancer: A review. *British Journal of Industrial Medicine* 16: 181-190, 1959.
- (73) DOLL, R., HILL, A. B. A study of the aetiology of carcinoma of the lung. *British Medical Journal* 2: 1271-1286, December 13, 1952.
- (74) DOLL, R., HILL, A. B. Mortality in relation to smoking: Ten years' observations of British doctors. (Part 1) *British Medical Journal* 1(5395): 1399-1410, May 30, 1964.
- (75) DOLL, R., HILL, A. B. Mortality in relation to smoking: Ten years' observations of British doctors. (Concluded) *British Medical Journal* 1(5396): 1460-1467, June 6, 1964.
- (76) DONTENWILL, W. Experimental investigations on the effect of cigarette smoke inhalation on small laboratory animals. IN: Hanna, M. G., Jr., Nettesheim, P., Gilbert, J. R. (Editors). *Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. U.S. Atomic Energy Commission Symposium Series 18, April 1970. pp. 389-412.*
- (77) DONTENWILL, W., WIEBECKE, B. Tracheal and pulmonary alterations following the inhalation of cigarette smoke by the golden hamster. IN: Severi, L. (Editor). *Lung Tumors in Animals. Perugia, Italy, Division of Cancer Research, University of Perugia, June 1966. pp. 519-526.*
- (78) DRUCKREY, H. Experimental investigations on the possible carcinogenic effects of tobacco smoking. *Acta Medica Scandinavica* 170 (Supplement 369): 24-42, 1961.
- (79) DRUCKREY, H., LANDSCHÜTZ, C., PREUSSMANN, R. Oesophagus-carcinome nach Inhalation von Methyl-butyl-nitrosamin (MBNA) an Ratten. (Carcinomas of the oesophagus, induced by inhalation of methyl-butyl-nitrosamine (MBNA) in rats.) *Zeitschrift für Krebsforschung* 71(2): 135-139, July 1968.
- (80) DRUCKREY, H., PREUSSMANN, R., BLUM, G., IVANKOVIC, S., AFKHAM, J. Erzeugung von Karzinomen der Speiseröhre durch unsymmetrische Nitrosamine. (Esophageal carcinomas induced by asymmetric nitrosamines.) *Naturwissenschaften* 50(3): 100-101, 1963.
- (81) DRUCKREY, H., PREUSSMANN, R., IVANKOVIC, S., SCHMAHL, D. Organotrope carcinogene Wirkungen bei 65 verschiedenen N-nitroso-Verbindungen an B1-Ratten. (Organotropic carcinogenic effects of 65 different N-nitroso compounds of B1-rats.) *Zeitschrift für Krebsforschung* 69(2): 103-201, March 22, 1967.
- (82) DRUCKREY, H., SCHILDBACH, A. Quantitative Untersuchungen zur Bedeutung des Benzpyrens für die carcinogene Wirkung von Tabakrauch. (Quantitative studies on the significance of benzo[a]pyrene for

- the carcinogenic effect of tobacco smoke.) Zeitschrift für Krebsforschung 65: 465-470, 1963.
- (83) DUNGAL, N. Lung carcinoma in Iceland. Lancet 2(6624): 245-247, August 12, 1950.
- (84) DUNHAM, L. J., HERROLD, K. M. Failure to produce tumors in the hamster cheek pouch by exposure to ingredients of betel-quid; histopathologic changes in the pouch and other organs by exposure to known carcinogens. Journal of the National Cancer Institute 29(6): 1047-1067, December 1962.
- (85) DUNHAM, L. J., RABSON, A. S., STEWART, H. L., FRANK, A. S., YOUNG, J. L., JR. Rates, interview, and pathology study of cancer of the urinary bladder in New Orleans, Louisiana. Journal of the National Cancer Institute 41(3): 683-709, September 1968.
- (86) DUTTA-CHOUDHURI, R., ROY, H., SEN GUPTA, B. K. Cancer of the larynx and hypopharynx. A clinicopathological study with special reference to aetiology. Journal of the Indian Medical Association 32(9): 352-362, May 1, 1959.
- (87) EBENIUS, B. Cancer of the lip. A clinical study of 778 cases with particular regard to predisposing factors and radium therapy. Acta Radiologica (Supplement 48): 1-232, 1943.
- (88) EISENBERG, H., CAMPBELL, P. C., FLANNERY, J. T. Cancer in Connecticut. Incidence characteristics 1935-1962. Hartford, Connecticut State Department of Health, 1967. 97 pp.
- (89) ELMENHORST, H., RECKZEH, G. Aromatische Kohlenwasserstoffe im Tabakrauch. (Aromatic hydrocarbons in tobacco smoke.) Beitrage zur Tabakforschung 2(5): 180-204, May 1964.
- (90) ELZAY, R. P. Effect of alcohol and cigarette smoke as promoting agents in hamster pouch carcinogenesis. Journal of Dental Research 48(6, Part 2): 1200-1205, November-December 1969.
- (91) EPSTEIN, S. S., ANDREA, J., JAFFEE, H., JOSHI, S., FALK, H., MANTEL, N. Carcinogenicity of the herbicide *maleic hydrazide*. Nature 215(5108): 1388-1390, September 23, 1967.
- (92) ESSENBERG, J. M. Cigarette smoke and the incidence of primary neoplasm of the lung in the albino mouse. Science 116: 561-562, November 21, 1952.
- (93) FALK, H. L., KOTIN, P., MEHLER, A. Polycyclic hydrocarbons as carcinogens in man. Archives of Environmental Health 8(5): 721-730, May 1964.
- (94) FERRI, E. S., BARATTA, E. J. Polonium-210 in tobacco, cigarette smoke and selected human organs. Public Health Reports 81(2): 121-127, February 1966.
- (95) FERRI, E. S., BARATTA, E. J. Polonium-210 in tobacco products and human tissues. Radiological Health Data and Reports 7(9): 485-488, September 1966.
- (96) FLETCHER, C. M., HORN, D. Smoking and health. WHO Chronicle 24(8): 345-370, August 1970.
- (97) FRIEDEL, G. H., BURNEY, S. W., BELL, J. R., SOTO, E. Pathology as related to tryptophan metabolite excretion, occupational history, and smoking habits in patients with bladder cancer. Journal of the National Cancer Institute 43(1): 303-306, July 1969.
- (98) GELFAND, M., GRAHAM, A. J. P., LIGHTMAN, S. Carcinoma of bronchus and the smoking habit in Rhodesian Africans. British Medical Journal 3(5616): 468-469, August 24, 1968.

- (99) GELLHORN, A. The cocarcinogenic activity of cigarette tobacco tar. *Cancer Research* 18(6) : 510-517, June 1958.
- (100) GOLDBLATT, M. W. Occupational carcinogenesis. *British Medical Bulletin* 14(2) : 136-140, 1958.
- (101) GRAHAM, E. A., CRONINGER, A. B., WYNDER, E. L. Experimental production of carcinoma with cigarette tar. IV. Successful experiments with rabbits. *Cancer Research* 17(11) : 1058-1066, December 1957.
- (102) GRAHAM, S. Cancer of lung related to smoking behavior. *Cancer* 21(3) : 523-530, March 1968.
- (103) GRAHAM, S., CROUCH, S., LEVIN, M. L., BOCK, F. G. Variations in amounts of tobacco tar retrieved from selected models of smoking behavior simulated by smoking machine. *Cancer Research* 23(7) : 1025-1030, August 1963.
- (104) GRAY, S. H., CORDONNIER, J. Early carcinoma of the lung. *A. M. A. Archives of Surgery* 19 : 1618-1626, 1929.
- (105) GREGORY, L. P. Polonium-210 in leaf tobacco from four countries. *Science* 150 : 74-76, October 1, 1965.
- (106) GROSS, P., DE TREVILLE, T. P., TOLKER, E. B., KASCHAK, M., BABYAK, M. A. Experimental asbestosis. The development of lung cancer in rats with pulmonary deposits of chrysotile asbestos dust. *Archives of Environmental Health* 15(3) : 343-355, September 1967.
- (107) GSELL, O. Carcinome bronchique et tabac. (Bronchial carcinoma and tobacco.) *Medecine et Hygiene* 12(279) : 429-431, December 1, 1954.
- (108) GUERIN, M. Tumeurs pulmonaires et cancer buccal chez le rat soumis a l'inhalation de fumee de sigarete. (Pulmonary tumors and oral cancers in rats subjected to inhalation of cigarette smoke.) *Bulletin de l'Association Francaise pour l'Etude du Cancer* 46(2) : 295-309, 1959.
- (109) GUERIN, M., CUZIN, J.-L. Action carcinogene du goudron de fumee de cigarette sur la peau de souris. (Carcinogenic action of tar from cigarette smoke on mouse skin.) *Bulletin de l'Association Francaise pour l'Etude du Cancer* 44(3) : 387-408, 1957.
- (110) GUIMARD, J. Alterations cellulaires provoques *in vitro*, sur des fibroblastes quiescents et en mitose, par des goudrons entiers de tabac. (Cellular changes induced *in vitro* in quiescent fibroblasts and those in mitosis by nonfractional tobacco tar.) *Archives des Sciences Physiologiques* 20(2) : 153-167, 1966.
- (111) GUTHRIE, F. E. The nature and significance of pesticide residues on tobacco and in tobacco smoke. *Beiträge zur Tabakforschung* 4(6) : 229-246, November 1968.
- (112) HAENSZEL, W., LOVELAND, D. B., SIRKEN, M. G. Lung-cancer mortality as related to residence and smoking histories. I. White males. *Journal of the National Cancer Institute* 28(4) : 947-1001, April 1962.
- (113) HAENSZEL, W., SHIMKIN, M. B. A retrospective study of lung cancer in women. *Journal of the National Cancer Institute* 21(5) : 825-842, November 1958.
- (114) HAENSZEL, W., SHIMKIN, M. B., MILLER, H. P. Tobacco smoking patterns in the United States. *Public Health Monograph No. 45*, May 1956. 111 pp.
- (115) HAENSZEL, W., TAEUBER, K. E. Lung-cancer mortality as related to residence and smoking histories. II. White females. *Journal of the National Cancer Institute* 32(4) : 803-838, April 1964.
- (116) HAMER, D., WOODHOUSE, D. L. Biological tests for carcinogenic action of tar from cigarette smoke. *British Journal of Cancer* 10 : 49-53, 1956.

- (117) HAMILTON, J. D., SEPP, A., BROWN, T. C., MACDONALD, F. W. Morphological changes in smokers' lungs. *Canadian Medical Association Journal* 77(3): 177-182, August 1, 1957.
- (118) HAMMOND, E. C. Smoking in relation to the death rates of 1 million men and women. IN: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. Bethesda, Md., U.S. Public Health Service, National Cancer Institute Monograph, No. 19, January 1966. pp. 127-204.
- (119) HAMMOND, E. C., AUERBACH, O., KIRMAN, D., GARFINKEL, L. Effects of cigarette smoking on dogs. I. Design of experiment, mortality and findings in lung parenchyma. *Archives of Environmental Health* 21(6): 740-753, December 1970.
- (120) HAMMOND, E. C., HORN, D. Smoking and death rates—report on forty-four months of follow-up of 187,783 men. II. Death rates by cause. *Journal of the American Medical Association* 166(11): 1294-1308, March 15, 1958.
- (121) HARRIS, R. J. C., NEGRONI, G. Production of lung carcinomas in C57BL mice exposed to a cigarette smoke and air mixture. *British Medical Journal* 4(5580): 637-641, December 16, 1967.
- (122) HERROLD, K. M., DUNHAM, L. J. Induction of carcinoma and papilloma of the tracheobronchial mucosa of the Syrian hamster by intratracheal instillation of benzo(a)pyrene. *Journal of the National Cancer Institute* 28(2): 467-491, February 1962.
- (123) HILL, C. R. Polonium-210 in man. *Nature* 208(5009): 423-428, October 30, 1965.
- (124) HIRAYAMA, T. An epidemiological study of oral and pharyngeal cancer in Central and Southeast Asia. *Bulletin of the World Health Organization* 34(1): 41-69, 1966.
- (125) HIRAYAMA, T. Smoking in relation to the death rates of 265,118 men and women in Japan. Tokyo, National Cancer Center, Research Institute, Epidemiology Division, September 1967. 14 pp.
- (126) HITOSUGI, M. Epidemiological study of lung cancer with special reference to the effect of air pollution and smoking habit. *Bulletin of the Institute of Public Health* 17(3): 237-256, September 1968.
- (127) HOFFMANN, D., MASUDA, Y., WYNDER, E. L. Alpha-naphthylamine and beta naphthylamine in cigarette smoke. *Nature* 221(5177): 254-256, January 18, 1969.
- (128) HOFFMANN, D., RATHKAMP, G. Chemical studies on tobacco smoke. V. Quantitative determination of chlorinated hydrocarbon insecticides in cigarette tobacco and its smoke. *Beiträge zur Tabakforschung* 4(5): 201-214, July 1968.
- (129) HOFFMANN, D., WYNDER, E. L. Chamber development and aerosol dispersion. IN: Hanna, M. G., Jr., Nettesheim, P., Gilbert, J. R. (Editors). *Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969*. U.S. Atomic Energy Commission Symposium Series 18, April 1970. pp. 173-191.
- (130) HOLSTI, L. R., ERMALA, P. Papillary carcinoma of the bladder in mice, obtained after peroral administration of tobacco tar. *Cancer* 8(4): 679-682, July-August 1955.
- (131) HOMBURGER, F., TREGER, A., BAKER, J. R. Mouse-skin painting with smoke condensates from cigarettes made of pipe, cigar, and cigarette

- tobaccos. *Journal of the National Cancer Institute* 31(6) : 1445-1459, December 1963.
- (132) HORIE, A., KOHCHI, S., KURATSUNE, M. Carcinogenesis in the esophagus. II. Experimental production of esophageal cancer by administration of ethanolic solution of carcinogens. *Gann* 56(5) : 429-441, October 1965.
- (133) HUEPER, W. C. Experimental studies in metal cancerigenesis. VI. Tissue reactions in rats and rabbits after parenteral introduction of suspensions of arsenic, beryllium, or asbestos in lanolin. *Journal of the National Cancer Institute* 15(1) : 113-129, August 1954.
- (134) HUEPER, W. C. Experimental studies in metal cancerigenesis. IX. Pulmonary lesions in guinea pigs and rats exposed to prolonged inhalation of powdered metallic nickel. *A.M.A. Archives of Pathology* 65 : 600-607, June 1958.
- (135) HUEPER, W. C., PAYNE, W. W. Experimental studies in metal carcinogenesis. Chromium, nickel, iron, arsenic. *Archives of Environmental Health* 5(5) : 445-462, November 1962.
- (136) HUEPER, W. C., WILEY, F. H., WOLFE, H. D., RANTA, K. E., LEMING, M. F., BLOOD, F. R. Experimental production of bladder tumors in dogs by administration of beta-naphthylamine. *Journal of Industrial Hygiene and Toxicology* 20(1) : 46-84, January 1938.
- (137) ISHII, K., NAKAMURA, K., OZAKI, H., YAMADA, N., TAKEUCHI, T. Suizogan no ekigaku ni okeru mondaiten. (Some aspects of the epidemiology of cancer of the pancreas.) *Nippon Rinsko* 26(8) : 1839-1842, August 1968.
- (138) JOHNSON, D. E., MILLAR, J. D., RHOADES, J. W. Nitrosamines in tobacco smoke. IN: Wynder, E. L., Hoffmann, D. (Editors). *Toward a Less Harmful Cigarette*. Bethesda, Md., U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute Monograph 28, June 1968. pp. 181-189.
- (139) KAHN, H. A. The Dorn study of smoking and mortality among U.S. veterans: Report on 8½ years of observation. IN: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. Bethesda, Md., U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966. pp. 1-125.
- (140) KELLER, A. Z. Cirrhosis of the liver, alcoholism and heavy smoking associated with cancer of the mouth and pharynx. *Cancer* 20(6) : 1015-1022, June 1967.
- (141) KELLER, A. Z. Cellular types, survival, race, nativity, occupations, habits and associated diseases in the pathogenesis of lip cancers. *American Journal of Epidemiology* 91(5) : 486-499, May 1970.
- (142) KELLEY, T. F. Polonium-210 content of mainstream cigarette smoke. *Science* 149(3683) : 537-538, July 30, 1965.
- (143) KERB, W. K., BARKIN, M., LEVERS, P. E., WOO, S. K.-C., MENCZYK, Z. The effect of cigarette smoking on bladder carcinogens in man. *Canadian Medical Association Journal* 93(1) : 1-7, July 3, 1965.
- (144) KIDA, H., OMOTO, T., SAKAMOTO, K., MOMOSE, S. Fukuoka ken hokubu ni okeru boko shuyo no ekigaku to kei. (Statistics and epidemiology of urinary bladder tumors in northern Fukuoka, Japan.) *Hifu to Hinyo* 30(5) : 883-889, October 1968.
- (145) KILIBARDA, M., PETROVIC, D., PANOV, D., DJURIC, D. Contamination with polonium-210, uranium and radium-226 due to smoking. *Health Physics* 12 : 1808, December 1966.

- (146) KIRYU, S., KURATSUNE, M. Polycyclic aromatic hydrocarbons in the cigarette tar produced by human smoking. *Gann* 57: 317-322, August 1966.
- (147) KNUDTSON, K. P. The pathologic effects of smoking tobacco on the trachea and bronchial mucosa. *American Journal of Clinical Pathology* 33(4): 310-317, April 1960.
- (148) KOCHEN, W., HOCHBERG, K. Untersuchungen über den Tryptophan-Stoffwechsel beim Blasen-Carcinom. (Studies about the tryptophan metabolism in the carcinoma of bladder.) *Zeitschrift für Krebsforschung* 73(3): 251-264, January 29, 1970.
- (149) KOTIN, P., FALK, H. L. Atmospheric factors in pathogenesis of lung cancer. *Advances in Cancer Research* 7: 475-514, 1963.
- (150) KOTIN, P., FALK, H. L. Polluted urban air and related environmental factors in the pathogenesis of pulmonary cancer. *Diseases of the Chest* 45(3): 236-246, March 1964.
- (151) KOULUMIES, M. Smoking and pulmonary carcinoma. *Acta Radiologica* 39: 255-260, 1953.
- (152) KRESHOVER, S. J. The effect of tobacco on epithelial tissues of mice. *Journal of the American Dental Association* 45(6): 528-540, November 1952.
- (153) KREYBERG, L. Histological Lung Cancer Types. A Morphological and Biological Correlation. *Acta Pathologica et Microbiologica Scandinavica* (Supplementum 157): 1962. 92 pp.
- (154) KREYBERG, L. Aetiology of Lung Cancer. A Morphological Epidemiological and Experimental Analysis. Oslo, Universitetsforlaget, 1969. 99 pp.
- (155) KUHN, H. Tobacco alkaloids and their pyrolysis products in the smoke. IN: Von Euler, U.S. (Editor). *Tobacco Alkaloids and Related Compounds*. New York, Macmillan, 1965. pp. 37-51.
- (156) KURATSUNE, M., KOHCHI, S., HORIE, A. Carcinogenesis in the esophagus. I. Penetration of benzo(a)pyrene and other hydrocarbons into the esophageal mucosa. *Gann* 56(2): 177-187, 1965.
- (157) KUSCHNER, M. The J. Burns Amberson Lecture. The causes of lung cancer. *American Review of Respiratory Diseases* 98(4): 573-590, October 1968.
- (158) LANCASTER, H. O. Cancer statistics in Australia. Part II. Respiratory system. *Medical Journal of Australia* 1: 1006-1011, June 30, 1962.
- (159) LASKIN, S., KUSCHNER, M., DREW, R. T. Studies in pulmonary carcinogenesis. IN: Hanna, M. G., Jr., Nettesheim, P., Gilbert, J. R. (Editors). *Inhalation Carcinogenesis*. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1968. U.S. Atomic Energy Commission Symposium Series 18, April 1970. pp. 321-351.
- (160) LASNITZKI, I. The effect of a hydrocarbon-enriched fraction from cigarette smoke on mouse tracheas grown *in vitro*. *British Journal of Cancer* 22(1): 105-109, March 1968.
- (161) LASNITZKI, I. The effect of a hydrocarbon-enriched fraction of cigarette smoke condensate on human fetal lung grown *in vitro*. *Cancer Research* 28(3): 516-513, March 1968.
- (162) LEDERMANN, S. Cancers, tabac, vin et alcool. (Cancers, tobacco, wine and alcohol.) *Concours Medical* 1: 1107, 1109-1111, 1113-1114, 1955.
- (163) LEE, A. M., FRAUMENI, J. F., JR. Arsenic and respiratory cancer in man: An occupational study. *Journal of the National Cancer Institute* 42(6): 1045-1052, June 1969.
- (164) LEUCHTENBERGER, C., LEUCHTENBERGER, R. The role of influenza virus in the development of malignant transformation *in vitro* and in the res-

- piratory tract of mice, with and without exposure to cigarette smoke. *Rivista di Biologia* 59: 445-463, 1966.
- (165) LEUCHTENBERGER, C., LEUCHTENBERGER, R. Cytologic and cytochemical effects on primary mouse kidney tissue and lung organ cultures after exposure to whole, fresh smoke and its gas phase from unfiltered, charcoal-filtered, and cigar tobacco cigarettes. *Cancer Research* 29(4): 862-872, April 1969.
- (166) LEUCHTENBERGER, C., LEUCHTENBERGER, R., DOOLIN, P. F. A correlated histological, cytological, and cytochemical study of the tracheobronchial tree and lungs of mice exposed to cigarette smoke. I. Bronchitis with atypical epithelial changes in mice exposed to cigarette smoke. *Cancer* 2(3): 490-506, May-June 1958.
- (167) LEUCHTENBERGER, C., LEUCHTENBERGER, R., ZEBRUN, W., SHAFFER, P. A correlated histological, cytological, and cytochemical study of the tracheobronchial tree and lungs of mice exposed to cigarette smoke. II. Varying responses of major bronchi to cigarette smoke, absence of bronchogenic carcinoma after prolonged exposure, and disappearance of bronchial lesions after cessation of exposure. *Cancer* 13(4): 721-732, July-August 1960.
- (168) LEUCHTENBERGER, R., LEUCHTENBERGER, C., ZEBRUN, W., SHAFFER, P. A correlated histological, cytological, and cytochemical study of the tracheobronchial tree and lungs of mice exposed to cigarette smoke. III. Unaltered incidence of grossly visible adenomatous lung tumors in female CF₁ mice after prolonged exposure to cigarette smoke. *Cancer* 13(5): 956-958, September-October 1960.
- (169) LEVIN, M. L., GOLDSTEIN, H., GERHARDT, P. R. Cancer and tobacco smoking. A preliminary report. *Journal of the American Medical Association* 143(4): 336-338, May 27, 1950.
- (170) LICKINT, F. Der Tabakrauch als Ursache des Lungenkrebses. Spezieller Teil IV. Ätiologie und Prophylaxe des Lungenkrebses. (Tobacco smoke as cause of lung cancer. Special Section IV. IN: Etiology and Prophylaxis of Lung Cancer.) Dresden, Theodor Steinkopff, 1953. pp. 66-141.
- (171) LILIENFELD, A. M., LEVIN, M. L., MOORE, G. E. The association of smoking with cancer of the urinary bladder in humans. *A.M.A. Archives of Internal Medicine* 98: 129-135, 1956.
- (172) LITTLE, J. B., RADFORD, E. P., JR. Polonium-210 in bronchial epithelium of cigarette smokers. *Science* 155(3762): 606-607, February 3, 1967.
- (173) LITTLE, J. B., RADFORD, E. P., JR., MCCOMBS, H. L., HUNT, V. R. Polonium-210 in lungs and soft tissues of cigarette smokers. *Radiation Research* 22: 209, 1964.
- (174) LITTLE, J. B., RADFORD, E. P., JR., MCCOMBS, H. L., HUNT, V. R. Distribution of Polonium-210 in pulmonary tissues of cigarette smokers. *New England Journal of Medicine* 273(25): 1343-1351, December 16, 1965.
- (175) LOCKWOOD, K. On the etiology of bladder tumors in Kobenhavn-Frederiksberg. An inquiry of 369 patients and 369 controls. *Acta Pathologica et Microbiologica Scandinavica* 51(Supplementum 145): 1961. 166 pp.
- (176) LOMBARD, H. L., SNEGIREFF, L. S. An epidemiological study of lung cancer. *Cancer* 12(2): 406-413, March-April 1959.
- (177) LORENZ, E., STEWART, H. L., DANIEL, J. H., NELSON, C. V. The effects of breathing tobacco smoke on strain A mice. *Cancer Research* 3: 123, 1943.

- (178) LUNDIN, F. E., JR., LLOYD, J. W., SMITH, E. M., ARCHER, V. E., HOLADAY, D. A. Mortality of uranium miners in relation to radiation exposure, hard-rock mining and cigarette smoking—1950 through September 1967. *Health Physics* 16(5) : 571-578, May 1969.
- (179) LYNCH, K. M., MCIVER, F. A., CAIN, J. R. Pulmonary tumors in mice exposed to asbestos dust. *A.M.A. Archives of Industrial Health* 15: 207-214, March 1957.
- (180) MCCONNELL, R. B., GORDON, K. C. T., JONES, T. Occupational and personal factors in the aetiology of carcinoma of the lung. *Lancet* 2: 651-656, October 4, 1952.
- (181) MAGEE, P. N., BARNES, J. M. Carcinogenic nitroso compounds. *Advances in Cancer Research* 10: 163-246, 1967.
- (182) MALTONI, C., CARRETTI, D., CANEPARI, C., GHETTI, G. Incidenza della metaplasia squamosa dell'epitelio respiratorio in rapporto al fumo di sigaretta. Studio citologico su 1000 individui di sesso maschile apparentemente sani. (Incidence of squamous metaplasia of the respiratory epithelium in relation to cigarette smoking. Cytological study on 1000 apparently healthy male individuals.) *Cancro* 21 (4) : 349-356, 1968.
- (183) MARTINEZ, I. Factors associated with cancer of the esophagus, mouth, and pharynx in Puerto Rico. *Journal of the National Cancer Institute* 42(6) : 1069-1094, June 1969.
- (184) MILLER, L., SMITH, W. E., BERLINER, S. W. Tests for effect of asbestos on benzo(a)pyrene carcinogenesis in the respiratory tract. *Annals of the New York Academy of Sciences* 132(Article 1) : 489-500, December 31, 1965.
- (185) MILLER, R. L., STEDMAN, R. L. Essential absence of beta-naphthylamine in cigarette smoke condensate. *Tobacco* 165(8) : 32, August 25, 1967.
- (186) MILLS, C. A., PORTER, M. M. Tobacco smoking habits and cancer of the mouth and respiratory system. *Cancer Research* 10: 539-542, 1950.
- (187) MILLS, C. A., PORTER, M. M. Tobacco smoking, motor exhaust fumes, and general air pollution in relation to lung cancer incidence. *Cancer Research* 17: 981-990, 1957.
- (188) MONTESANO, R., SAFFIOTTI, U. Carcinogenic response of the hamster respiratory tract to single subcutaneous administrations of diethylnitrosamine at birth. *Journal of the National Cancer Institute* 44(2) : 413-417, February 1970.
- (189) MONTESANO, R., SAFFIOTTI, U., SHUBIK, P. The role of topical and systemic factors in experimental respiratory carcinogenesis. IN: Hanna, M. G., Jr., Nettesheim, P., Gilbert, J. R. (Editors). *Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. U.S. Atomic Energy Commission Symposium Series 18, April 1970, pp. 353-371.*
- (190) MOORE, C. Multiple mouth-throat cancer. *American Journal of Surgery* 110(4) : 534-536, October 1965.
- (191) MOORE, C., CHRISTOPHERSON, W. M. The effect of cigarette-smoke condensate on hamster tissues. Exteriorized oral pouch and skin. *A.M.A. Archives of Surgery* 84(4) : 425-431, April 1962.
- (192) MOORE, C., MILLER, A. J. Effect of cigarette tar on the hamster pouch. *A.M.A. Archives of Surgery* 76(5) : 786-793, May 1958.
- (193) MOORE, G. E., BISSENGER, L. L., PROEHL, E. C. Intraoral cancer and the use of chewing tobacco. *Journal of the American Geriatrics Society* 1: 497-506, 1953.

- (194) MORGAN, J. G. Some observations on the incidence of respiratory cancer in nickel workers. *British Journal of Industrial Medicine* 15: 224-234, 1958.
- (195) MUHLBOCK, O. Carcinogene Werking van Sigarettenrook bij Muizen. (Carcinogenic action of cigarette smoke in mice). *Nederlands Tijdschrift voor Geneeskunde* 99(31): 2276-2278, July 30, 1955.
- (196) MULLER, F. H. Tabakmissbrauch und Lungencarcinom. (Tobacco misuse and lung carcinoma). *Zeitschrift für Krebsforschung* 49 (1): 57-85, 1939.
- (197) MUNOZ, N., CORREA, P., BOCK, F. G. Comparative carcinogenic effect of two types of tobacco. *Cancer* 21(3): 376-389, March 1968.
- (198) NASIELL, M. The Epithelial Picture in the Bronchial Mucosa in Chronic Inflammatory and Neoplastic Lung Disease and its Relation to Smoking. A comparative histologic and sputum-cytologic study. Stockholm, Cytology Laboratory, Department of Pathology at Sabbatsberg Hospital, Karolinska Institutet, 1968. 72 pp.
- (199) NELSON, N. Inhalation carcinogenesis in man: Environmental and occupational hazards. IN: Hanna, M. G., Jr., Nettesheim, P., Gilbert, J. R. (Editors). *Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. U. S. Atomic Energy Commission Symposium Series 18, April 1970.* pp. 3-12.
- (200) NETTESHEIM, P., HANNA, M. G., JR., DOHERTY, D. G., NEWELL, R. F., HELLMAN, A. Effects of chronic exposure to artificial smog and chromium oxide dust on the incidence of lung tumors in mice. IN: Hanna, M. G., Jr., Nettesheim, P., Gilbert, J. R. (Editors). *Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. U.S. Atomic Energy Commission Symposium Series No. 18, April 1970.* pp. 305-320.
- (201) NEURATH, G. Zur Frage des Vorkommens von N-Nitroso-Verbindungen im Tabakrauch. (Occurrence of n-Nitroso compounds in tobacco smoke.) *Experientia* 23(5): 400-404, 1967.
- (202) NEURATH, G. Stickstoffverbindungen des Tabakrauches. (Nitrogen compounds in tobacco smoke.) *Arzneimittel-Forschung* 19(7): 1093-1106, July 1969.
- (203) OCHSNER, A., DE BAKEY, M. Primary pulmonary malignancy. Treatment by total pneumonectomy. Analysis of 79 collected cases and presentation of 7 personal cases. *Surgery, Gynecology and Obstetrics* 68: 435-451, 1939.
- (204) ORMOS, J., KARACSONYI, G., BILICZKI, F., SZONYI, F. Lung cancer in the Hungarian plain. *Neoplasma* 16(6): 667-675, 1969.
- (205) ORR, J. W., WOODHOUSE, D. L., HAMER, D., MARCHANT, J., HOWELL, J. S. Cigarette tobacco tars. *British Empire Cancer Campaign Annual Report* 33: 238-239, 1955.
- (206) OTTO, H. Experimentelle Untersuchungen an Mäusen mit passiver Zigarettenrauchbeatmung. (Experimental investigations on mice through passive inhalation of cigarette smoke.) *Frankfurter Zeitschrift für Pathologie* 73: 10-23, 1963.
- (207) PAILER, M., HUBSCH, W. J., KUHN, H. Untersuchung der aliphatischen und aromatischen primären und sekundären Amine des Zigarettenrauches mit Hilfe der Gaschromatographie und Massenspektrometrie. (Study of the aliphatic and aromatic primary and secondary amines of cigarette smoke by gas chromatography and mass spectrometry.)

Fachliche Mitteilungen der Oesterreichischen Tabakregie No. 7: 109-118, April 1967.

- (208) PAPANICOLAOU, G. N., KOPROWSKA, I. Carcinoma-*in-situ* of the right lower bronchus: A case report. *Cancer* 4(1): 141-146, January 1951.
- (209) PASSEY, R. D., ROE, E. M. F., MIDDLETON, F. C., BERGEL, F., EVERETT, J. L., LEWIS, G. E., MARTIN, J. B., BOYLAND, E., SIMS, P. Cigarette smoking and cancer. *British Empire Cancer Campaign Annual Report* 32: 60-62, 1954.
- (210) PEACOCK, E. E., JR., GREENBERG, B. G., BRAWLEY, B. W. The effect of snuff and tobacco on the production of oral carcinoma: An experimental and epidemiological study. *Annals of Surgery* 151(4): 542-550, April 1960.
- (211) PERNU, J. An epidemiological study on cancer of the digestive organs and respiratory system. A study based on 7,078 cases. *Annales Medicinæ Internæ Fenniae* 49 (Supplement 33): 1960. 117 pp.
- (212) POTTER, E. A., TULLY, M. R. The statistical approach to the cancer problem in Massachusetts. *American Journal of Public Health and the Nation's Health* 35: 485-490, May 1945.
- (213) PROTZEL, M., GIARDINA, A. C., ALBANO, E. H. The effect of liver imbalance on the development of oral tumors in mice following the application of benzpyrene or tobacco tar. *Oral Surgery, Oral Medicine and Oral Pathology* 18(5): 622-635, November 1964.
- (214) QUAGLIARIELLO, E., TANCREDI, F., FEDELE, L., SACCONI, C. Tryptophan-nicotinic acid metabolism in patients with tumours of the bladder. Changes in the excretory products after treatment with nicotinamide and vitamin B₆. *British Journal of Cancer* 15: 367-372, 1961.
- (215) RADFORD, E. P., JR., HUNT, V. R. Polonium-210: A volatile radio-element in cigarettes. *Science* 143(3603): 247-249, January 17, 1964.
- (216) RADFORD, E. P., HUNT, V. R., LITTLE, J. B. Carcinogenicity of tobacco-smoke constituents. *Science* 165(3890): 312, July 18, 1969.
- (217) RAJEWSKY, B., STAHLHOFEN, W. Polonium-210 activity in the lungs of cigarette smokers. *Nature* 209(5030): 1312-1313, March 26, 1966.
- (218) RANDIG, K. Untersuchungen zur Ätiologie des Bronchialkarzinoms. (Investigations on the etiology of bronchial carcinoma.) *Öffentliche Gesundheitsdienst* 16(9): 305-313, December 1954.
- (219) REDDY, D. G., ANGULI, V. C. Experimental production of cancer with betel nut, tobacco and slaked lime mixture. *Journal of the Indian Medical Association* 49(7): 315-318, October 1, 1967.
- (220) REINGOLD, I. M., OTTOMAN, R. E., KONWALER, B. E. Bronchogenic carcinoma: A study of 60 necropsies. *American Journal of Clinical Pathology* 20: 515-525, 1950.
- (221) RIGDON, R. H. Effect of tobacco condensate on respiratory tract of white Pekin ducks. *A.M.A. Archives of Pathology* 69(1): 55-63, January 1960.
- (222) ROBBINS, W. T. Bronchial epithelium in smoking and nonsmoking college students. *Journal of the American College Health Association* 14(4): 265-266, April 1966.
- (223) ROCKEY, E. E., SPEER, F. D. The ill effects of cigarette smoking in dogs. *International Surgery* 46(6): 520-530, December 1966.
- (224) ROCKEY, E. E., SPEER, F. D., THOMPSON, S. A., AHN, K. J., HIROSE, T. Experimental study on effect of cigarette smoke condensate on bronchial mucosa. *Journal of the American Medical Association* 182 (11): 1094-1098, December 15, 1962.

- (225) ROE, F. J. C. Role of 3,4-benzopyrene in carcinogenesis by tobacco smoke condensate. *Nature* 194(4833) : 1089-1090, June 16, 1962.
- (226) ROTH, D., FREDRICKSON, D. T., OPPENHEIM, A., LONDON, M. Bioassay of the effects of smoking on DNA content of human respiratory epithelium. *Cancer* 21(6) : 1132-1136, June 1968.
- (227) ROTH, D., OPPENHEIM, A., FREDRICKSON, D. T. DNA-dependent dye binding by oral epithelium. Its relation to smoking habits. *Archives of Environmental Health* 17(1) : 59-61, July 1968.
- (228) ROYAL COLLEGE OF PHYSICIANS. Air pollution and Health. Summary and Report on Air Pollution and Its Effect on Health. By the Committee of the Royal College of Physicians of London on Smoking and Atmospheric Pollution. Pitman Medical and Scientific Publishing Co., Ltd., London, 1970. 80 pp.
- (229) ROZENBILDS, J. G. Carcinoma of the larynx and hypopharynx in South Australia 1952-1966. *Medical Journal of Australia* 2(6) : 244-249, August 5, 1967.
- (230) RUNECKLES, V. C. Natural radioactivity in tobacco and tobacco smoke. *Nature* 191(4786) : 322-325, July 22, 1961.
- (231) SACCOMANNO, G. Radiation exposure of uranium miners. U.S. Congress. Radiation Standards for Uranium Mining. Hearings before the Subcommittee on Research, Development, and Radiation of the Joint Committee On Atomic Energy, Congress of the United States. 91st Congress, 1st Session, March 17, and 18, 1969. pp. 301-315.
- (232) SADOWSKY, D. A., GILLIAM, A. G., CORNFIELD, J. The statistical association between smoking and carcinoma of the lung. *Journal of the National Cancer Institute* 13: 1237-1258, 1953.
- (233) SAFFIOTTI, U. Experimental respiratory tract carcinogenesis. *Progress in Experimental Tumor Research* 11: 302-333, 1969.
- (234) SAFFIOTTI, U. Experimental respiratory tract carcinogenesis and its relation to inhalation exposures. IN: Hanna, M. G., Jr., Nettesheim, P., Gilbert, J. R. (Editors). *Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. U.S. Atomic Energy Commission Symposium Series 18, April 1970.* pp. 27-54.
- (235) SAFFIOTTI, U., CEFIS, F., KOLB, L. H. A method for the experimental induction of bronchogenic carcinoma. *Cancer Research* 28(1) : 104-124, January 1968.
- (236) SAFFIOTTI, U., CEFIS, F., MONTESANO, R., SELLAKUMAR, A. R. Induction of bladder cancer in hamsters fed aromatic amines. Chapter 10. IN: DEICHMANN, W. B., LAMPE, K. L. (Editors). *Bladder Cancer. Proceedings of the 5th Inter-American Conference on Toxicology and Occupational Medicine. Coral Gables, University of Miami, School of Medicine, 1967.* pp. 129-135.
- (237) SAFFIOTTI, U., CEFIS, F., SHUBIK, P. Histopathology and histogenesis of lung cancer induced in hamsters by carcinogens carried by dust particles. In: Severi, L. (Editor). *Lung Tumors in Animals. Perugia, Division of Cancer Research, University of Perugia, June 1966.* pp. 537-546.
- (238) SALLEY, J. J. Experimental carcinogenesis in the cheek pouch of the Syrian hamster. *Journal of Dental Research* 33(2) : 253-262, April 1954.
- (239) SALLEY, J. J. Smoking and oral cancer. *Journal of Dental Research* 42 (Supplement to No. 1) : 328-339, 1963.

- (240) SANDERUD, K. Squamous metaplasia of the respiratory tract epithelium: An autopsy study of 214 cases. 2. Relation to tobacco smoking, occupation, and residence. *Acta Pathologica et Microbiologica Scandinavica* 43(1): 47-61, 1958.
- (241) SANGHVI, L. D., RAO, K. C. M., KHANOLKAR, V. R. Smoking and chewing of tobacco in relation to cancer of the upper alimentary tract. *British Medical Journal* 1: 1111-1114, May 7, 1955.
- (242) SCHARIRE, E., SCHONIGER, F. Lungenkrebs und Tabakverbrauch. (Lung cancer and smoking.) *Zeitschrift für Krebsforschung* 54: 261-269, 1943.
- (243) SCHLEGEL, J. U., PIPKIN, G., BANOWSKY, I. Urine composition in the etiology of bladder tumor formation. *Journal of Urology* 97(3): 479-481, March 1967.
- (244) SCHLEGEL, J. U., PIPKIN, G. E., NISHIMURA, R., DUKE, G. A. Studies in the etiology and prevention of bladder carcinoma. *Journal of Urology* 101(3): 317-324, March 1969.
- (245) SCHLEGEL, J. U., PIPKIN, G. E., SHULTZ, G. N. The aetiology of bladder tumours. *British Journal of Urology* 41(6): 718-723, December 1969.
- (246) SCHREK, R., BAKER, L. A., BALLARD, G. P., DOLGOFF, S. Tobacco smoking as an etiologic factor in disease. I. Cancer. *Cancer Research* 10: 49-58, 1950.
- (247) SCHWARTZ, D., DENOIX, P.-F. L'enquete francaise sur l'étiologie du cancer broncho-pulmonaire. Role du tabac. (French investigation on the etiology of bronchopulmonary cancer. Role of tobacco.) *Semaine des Hopitaux de Paris* 33 (62/7): 3630-3643, October 30, 1957.
- (248) SCHWARTZ, D., DENOIX, P.-F., ANGUERA, G. Recherche des localisations du cancer associees aux facteurs tabac et alcool chez l'homme. (Research on the localizations of cancer associates with tobacco and alcoholic factors in man.) *Bulletin de l'Association Francaise pour l'Etude du Cancer* 44: 336-361, 1957.
- (249) SCHWARTZ, D., FLAMANT, R., LELLOUCH, J., DENOIX, P.-F. Results of a French survey on the role of tobacco, particularly inhalation, in different cancer sites. *Journal of the National Cancer Institute* 26 (5): 1085-1108, May 1961.
- (250) SEGI, M., FUKUSHIMA, I., FUJISAKU, S., KURIHARA, M., SAITO, S., ASANO, K., KAMOI, M. An epidemiological study on cancer in Japan. The report of the Committee for Epidemiological study on Cancer, Sponsored by the Ministry of Welfare and Public Health. *Gann* 48 (Supplement): April 1957. 63 pp.
- (251) SELIKOFF, I. J., BADER, R. A., BADER, M. E., CHURG, J., HAMMOND, E. C. Asbestosis and neoplasia. *American Journal of Medicine* 42(4): 487-496, April 1967.
- (252) SELIKOFF, I. J., HAMMOND, E. C., CHURG, J. Asbestos exposure, smoking, and neoplasia. *Journal of the American Medical Association* 204(2): 106-112, April 8, 1968.
- (253) SERFONTEIN, W. J., HURTER, P. Nitrosamines as environmental carcinogens. II. Evidence for the presence of nitrosamines in tobacco smoke condensate. *Cancer Research* 26(4, Part 1): 575-579, April 1966.
- (254) SERFONTEIN, W. J., SMIT, J. H. Evidence for the occurrence of N-nitrosamines in tobacco. *Nature* 214(5084): 169-170, April 8, 1967.
- (255) SHANTA, V., KRISHNAMURTHI, S. Further studies in aetiology of carcinomas of the upper alimentary tract. *British Journal of Cancer* 17(1): 8-23, March 1963.

- (256) SHANTA, V., KRISHNAMURTHI, S. Further studies in etiology of carcinomas of the upper alimentary tract. *Acta; Unio Internationalis contra Cancrum* 20: 586-594, 1964.
- (257) SILVERMAN, S., JR., GALANTE, M. Oral Cancer. University of California, San Francisco Medical Center, January 1970. 56 pp.
- (258) SPAIN, D. M., BRADESS, V. A., TARTER, R., MATERO, A. Metaplasia of bronchial epithelium. Effect of age, sex, and smoking. *Journal of the American Medical Association* 211(8): 1331-1334, February 23, 1970.
- (259) STASZEWSKI, J. Palenie a rak wargi, jamy ustnej, migdalkow i krtani. (Tobacco smoking and its relation to cancer of the mouth, tonsils and larynx.) *Nowotwory* 10(2): 121-132, 1960.
- (260) STASZEWSKI, J. Palenie tytoniu a rak przelyku i zoladka oraz choroba wrzodowa. (Smoking and its relation to carcinoma of the upper digestive tract (esophagus and stomach) and to peptic ulcer.) *Polski Tygodnik Lekarski* 16(16): 287-292, May 4, 1960.
- (261) STASZEWSKI, J. Smoking and cancer of the urinary bladder in males in Poland. *British Journal of Cancer* 20(1): 32-35, March 1966.
- (262) STEDMAN, R. L. The chemical composition of tobacco and tobacco smoke. *Chemical Reviews* 68(2): 153-207, April 1968.
- (263) STOCKS, P. Cancer incidence in North Wales and Liverpool region in relation to habits and environment. *British Empire Cancer Campaign Annual Report* 35 (Supplement to Part 2): 66-95, 1957.
- (264) STOCKS, P. Recent epidemiological studies of lung cancer mortality, cigarette smoking and air pollution, with discussion of a new hypothesis of causation. *British Journal of Cancer* 20(4): 595-623, December 1966.
- (265) STOCKS, P., CAMPBELL, J. M. Lung cancer death rates among non-smokers and pipe and cigarette smokers. *British Medical Journal* 2: 923-929, October 15, 1955.
- (266) SUGIURA, K. Experimental production of carcinoma in mice with cigarette smoke tar. *Gann* 47(2): 243-244, June 1956.
- (267) SUNDERMAN, F. W., DONNELLY, A. J. Studies of nickel carcinogenesis metastasizing pulmonary tumors in rats induced by the inhalation of nickel carbonyl. *American Journal of Pathology* 46(6): 1027-1041, June 1965.
- (268) SUNDERMAN, F. W., DONNELLY, A. J., WEST, B., KINCAID, J. F. Nickel poisoning. IX. Carcinogenesis in rats exposed to nickel carbonyl. *A.M.A. Archives of Industrial Health* 20(1): 36-41, July 1959.
- (269) SUNDERMAN, F. W., KINCAID, J. F., DONNELLY, A. J., WEST, B. Nickel poisoning. IV. Chronic exposure of rats to nickel carbonyl. A report after one year of observation. *A.M.A. Archives of Industrial Health* 16(6): 480-485, December 1957.
- (270) SUNDERMAN, F. W., SUNDERMAN, F. W., JR. Nickel poisoning. XI. Implication of nickel as a pulmonary carcinogen in tobacco smoke. *American Journal of Clinical Pathology* 35(3): 203-209, March 1961.
- (271) SVOBODA, V. An analysis of some possible epidemiological factors involved in carcinoma of the larynx. *Neoplasma* 15(6): 677-684, 1968.
- (272) TAKANO, K., OSOGOSHI, K., KAMIMURA, N., KANDA, K., KANE, K., KAMIYAMA, R., SAKAMOTO, K., SATO, H., SHIRAI, Y., SEI, M., TANABE, T., HORINO, M., MINAMI, Y., MOTOJI, H., MORITA, R., ORIHATA, H., HIRAYAMA, T. Shokudogan no ekigaku, toku ni atsui inshokubutsu, inshu, kitsuen narabi ni eiyo ketsubo ni tsuite. (Epidemiology of cancer of the esophagus, with particular reference to the effect of hot

- food and drink, drinking, smoking, and nutritional deficiencies.) *Nippon Rinsho* 26(8) : 1823-1828, August 1968.
- (273) TARJAN, R., KEMENY, T. Multigeneration studies on DDT in mice. *Food and Cosmetic Toxicology* 7: 215-222, 1969.
- (274) TERRACOL, J., CALVET, J., MARQUES, P., COLL, J. Le tabac et le cancer du larynx. (Tobacco and cancer of the larynx.) *Vie Medicale* 48: 1149-1150, August 1967.
- (275) THAYER, P. S., KENSLER, C. J. Cigarette smoke: Charcoal filters reduce components that inhibit growth of cultured human cells. *Science* 146 (3644) : 642-644, October 30, 1964.
- (276) THORARINSSON, H., HALLGRIMSSON, J., BJARNASON, O., PETERSEN, G. Carcinoma of the lung in Iceland. *Diseases of the Chest* 52(6) : 754-759, December 1967.
- (277) TIPTON, D. L., CROCKER, T. T. Duration of bronchial squamous metaplasia produced in dogs by cigarette smoke condensate. *Journal of the National Cancer Institute* 33(3) : 487-495, September 1964.
- (278) TYLECOTE, F. E. Cancer of the lung. *Lancet* 2: 256-257, July 30, 1927.
- (279) UMIKER, W., STOREY, C. Bronchogenic carcinoma-*in-situ*. Report of a case with positive biopsy, cytological examination, and lobectomy. *Cancer* 5(2) : 369-374, March 1952.
- (280) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health. Washington, U.S. Department of Health, Education, and Welfare, December 1969. 677 pp.
- (281) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Changes in cigarette smoking habits between 1955 and 1966. Washington, U.S. Department of Health, Education, and Welfare, Vital and Health Statistics Series 10, Number 59, Public Health Service Publication No. 1000, April 1970. 33 pp.
- (282) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Mortality from diseases associated with smoking: United States, 1950-64. Washington, U.S. Department of Health, Education, and Welfare, Vital and Health Statistics Series 20, No. 4, Public Health Service Publication No. 1000, October 1966. 45 pp.
- (283) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Vital Statistics of the United States—1961. Vol. II—Mortality, Part A. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication, 1964.
- (284) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Vital Statistics of the United States—1962. Vol. II—Mortality, Part A. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication, 1964.
- (285) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Vital Statistics of the United States—1963. Vol. II—Mortality, Part A. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication, 1965.
- (286) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Vital Statistics of the United States—1964. Vol. II—Mortality, Part A. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication, 1966.
- (287) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Vital Statistics of the United States—1965. Vol. II—Mortality,

- Part A. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication, 1967.
- (288) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Vital Statistics of the United States—1966. Vol. II—Mortality, Part A. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication, 1968.
- (289) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Vital Statistics of the United States—1967. Vol. II—Mortality, Part A. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication, 1969.
- (290) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Vital Statistics Rates in the United States 1940–1960. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1677, 1968. 881 pp.
- (291) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.
- (292) VALKO, P. Koureni a vyskyt zhoubnych novotvaru hrtanu. (Smoking and occurrence of malignant tumors of the larynx.) *Ceskoslovenska Otolaryngologie* 1: 102–105, 1952.
- (293) VAN DUUREN, B. L. Tobacco carcinogenesis. *Cancer Research* 28(11): 2357–2362, November 1968.
- (294) VAN DUUREN, B. L., SIVAK, A., LANGSETH, L., GOLDSCHMIDT, B. M., SEGAL, A. Initiators and promoters in tobacco carcinogenesis. IN: Wynder, E. L., Hoffmann, D. (Editors). *Toward a Less Harmful Cigarette*. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 28, June 1968. pp. 173–180.
- (295) VAN DUUREN, B. L., SIVAK, A., GOLDSCHMIDT, B. M., KATZ C., MELCHIONNE, S. Initiating activity of aromatic hydrocarbons in two-stage carcinogenesis. *Journal of the National Cancer Institute* 44(5): 1167–1173, May 1970.
- (296) VAN DUUREN, B. L., SIVAK, A., SEGAL, A., ORRIS, L., LANGSETH, L. The tumor-promoting agents of tobacco leaf and tobacco smoke condensate. *Journal of the National Cancer Institute* 37(4): 519–526, October 1966.
- (297) VINCENT, R. G., MARCHETTA, F. The relationship of the use of tobacco and alcohol to cancer of the oral cavity, pharynx or larynx. *American Journal of Surgery* 106(3): 501–505. September 1963.
- (298) VOGLER, W. R., LLOYD, J. W., MILMORE, B. K. A retrospective study of etiological factors in cancer of the mouth, pharynx, and larynx. *Cancer* 15(2): 246–258, March–April 1962.
- (299) WAGONER, J. K., ARCHER, V. E., CARROLL, B. E., HOLADAY, D. A., LAWRENCE, P. A. Cancer mortality patterns among U.S. uranium miners and millers, 1950 through 1962. *Journal of the National Cancer Institute* 32(4): 787–801, April 1964.
- (300) WAGONER, J. K., ARCHER, V. E., LUNDIN, F. E., JR., HOLADAY, D. A., LLOYD, J. W. Radiation as the cause of lung cancer among uranium miners. *New England Journal of Medicine* 273(4): 181–188, July 22, 1965.
- (301) WAGONER, J. K., MILLER, R. W., LUNDIN, F. E., JR., FRAUMENI, J. F., JR., HAIJ, M. E. Unusual cancer mortality among a group of underground metal miners. *New England Journal of Medicine* 269(6): 284–289, August 8, 1963.

- (302) WAHI, P. N., KEHAR, U., LAHIRI, B. Factors influencing oral and oropharyngeal cancers in India. *British Journal of Cancer* 19(4) : 642-660, December 1965.
- (303) WAINGROW, S. M., HORN, D., IKARD, F. F. Dosage patterns of cigarette smoking in American adults. *American Journal of Public Health and the Nation's Health* 58(1) : 54-70, January 1968.
- (304) WASSINK, W. F. Ontstaansvoorwaarden voor longkanker. (Conditions for the origin of lung cancer.) *Nederlands Tijdschrift voor Geneeskunde* 92(46) : 3732-3747, November 13, 1948.
- (305) WATSON, W. L., CONTE, A. J. Smoking and lung cancer. *Cancer* 7(2) : 245-249, March 1954.
- (306) WEIR, J. M., DUNN, J. E., JR. Smoking and mortality: A prospective study. *Cancer* 25(1) : 105-112, January 1970.
- (307) WEISBURGER, J. H., WEISBURGER, E. K. Tests for chemical carcinogens. IN: Busch, H. (Editor). *Methods in Cancer Research*. New York, Academic Press, 1967. pp. 307-398.
- (308) WICKEN, A. J. Environmental and Personal Factors in Lung Cancer and Bronchitis Mortality in Northern Ireland, 1960-62. London, Tobacco Research Council, Research Paper No. 9, 1966. 84 pp.
- (309) WILLIAMS, M. J. Extensive carcinoma-*in-situ* in the bronchial mucosa associated with two invasive bronchogenic carcinomas. Report of case. *Cancer* 5(4) : 740-747, July 1952.
- (310) WYNDER, E. L., BROSS, I. J. A study of etiological factors in cancer of the esophagus. *Cancer* 14(2) : 389-413, March-April 1961.
- (311) WYNDER, E. L., BROSS, I. J., CORNFIELD, J., O'DONNELL, W. E. Lung cancer in women. A study of environmental factors. *New England Journal of Medicine* 255(24) : 1111-1121, December 13, 1956.
- (312) WYNDER, E. L., BROSS, I. J., DAY, E. A study of environmental factors in cancer of the larynx. *Cancer* 9(1) : 86-110, January-February 1956.
- (313) WYNDER, E. L., BROSS, I. J., FELDMAN, R. M. A study of the etiological factors in cancer of the mouth. *Cancer* 10(6) : 1300-1323, November-December 1957.
- (314) WYNDER, E. L., CORNFIELD, J. Cancer of the lung in physicians. *New England Journal of Medicine* 248(11) : 441-444, March 12, 1953.
- (315) WYNDER, E. L., DODO, H., BLOCH, D. A., GANTT, R. C., MOORE, O. S. Epidemiologic investigation of multiple primary cancer of the upper alimentary and respiratory tracts. *Cancer* 24(4) : 730-739, October 1969.
- (316) WYNDER, E. L., GRAHAM, E. A. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma. A study of six hundred and eighty-four proved cases. *Journal of the American Medical Association* 143(4) : 329-336, May 27, 1950.
- (317) WYNDER, E. L., GRAHAM, E. A., CRONINGER, A. B. Experimental production of carcinoma with cigarette tar. *Cancer Research* 13: 855-864, 1953.
- (318) WYNDER, E. L., GRAHAM, E. A., CRONINGER, A. B. Experimental production of carcinoma with cigarette tar. II. Test with different mouse strains. *Cancer Research* 15: 445-448, 1955.
- (319) WYNDER, E. L., HOFFMANN, D. Tobacco and Tobacco Smoke. *Studies in Experimental Carcinogenesis*. New York, Academic Press, 1967. 730 pp.
- (320) WYNDER, E. L., HOFFMANN, D. Experimental tobacco carcinogenesis. *Science* 162(3856) : 862-871, November 22, 1968.

- (321) WYNDER, E. L., HOFFMANN, D. A study of tobacco carcinogenesis. X. Tumor promoting activity. *Cancer* 24(2) : 289-301, August 1969.
- (322) WYNDER, E. L., HULTBERG, S., JACOBSSON, F., BROSS, I. J. Environmental factors in cancer of the upper alimentary tract. A Swedish study with special reference to Plummer-Vinson (Paterson-Kelly) syndrome. *Cancer* 10(3) : 470-487, May-June 1957.
- (323) WYNDER, E. L., KOPF, P., ZIEGLER, H. A study of tobacco carcinogenesis. II. Dose-response studies. *Cancer* 10(6) : 1193-1200, November-December 1957.
- (324) WYNDER, E. L., MAUBUCH, K., BEATTIE, E. J., JR. The epidemiology of lung cancer. Recent trends. *Journal of the American Medical Association* 213(13) : 2221-2228, September 28, 1970.
- (325) WYNDER, E. L., NAVARRETE, A., AROSTEGUI, G. E., LLAMBES, J. L. Study of environmental factors in cancer of the respiratory tract in Cuba. *Journal of the National Cancer Institute* 20(4) : 665-673, April 1958.
- (326) WYNDER, E. L., ONDERDONK, J., MANTEL, N. An epidemiological investigation of cancer of the bladder. *Cancer* 16(11) : 1388-1407, November 1963.
- (327) WYNDER, E. L., TAGUCHI, K. T., BADEN, V., HOFFMANN, D. Tobacco carcinogenesis. IX. Effect of cigarette smoke on respiratory tract of mice after passive inhalation. *Cancer* 21(1) : 134-153, January 1968.
- (328) WYNDER, E. L., WRIGHT, G. A study of tobacco carcinogenesis. I. The primary fractions. *Cancer* 10(2) : 255-271, March-April 1957.
- (329) YOSHIDA, O., BROWN, R. R., BRYAN, G. T. Relationship between tryptophan metabolism and heterotopic recurrences of human urinary bladder tumors. *Cancer* 25(4) : 773-780, April 1970.
- (330) YOSHIDA, O., MIYAKAWA, M., HARADA, T., OKADA, K. Bokogan no ekigaku ni okeru mondaiten. (Some aspects of the epidemiology of urinary bladder cancer.) *Nippon Rinsho* 26(8) : 1850-1854, August 1968.

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, Nether- lands (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 hos- pital 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 strati- fied by degree of air pollution.	Cases: Relatives queried by mail question- naire or personal visit. Controls: House-to-house interviews.

TABLE A3.—Outline of methods used in retrospective studies of smoking in relation to lung cancer (cont.)

Author, year, country, reference	Sex of cases	Number of persons and method of selection		Collection of data
		Cases	Controls	
Levin et al., 1950, U.S.A. (169).	M	236 cancer hospital patients with diagnosed lung cancer.	481 patients in same hospital with nonmalignant diagnoses.	Cases and Controls: Routine clinical history taken before diagnosis.
Wynder and Graham, 1950, U.S.A. (316).	M-F	605 hospital and private lung cancer patients in many cities.	780 patients of several hospitals with diagnoses other than lung cancer.	Nearly all data by personal interview; a few cases by questionnaire; a few from intimate acquaintances. Some interviews with knowledge or presumption of diagnosis, some with none. 595 diagnosed by tissue examination, nine by sputum, and one by pleural fluid examination.
McConnell et al., 1952, England, (180).	M-F	100 lung cancer patients, unselected, in 3 hospitals in Liverpool area.	200 inpatients of same hospitals, matched by age and sex, without cancer.	Personal interviews by the authors of both cases and controls.
Doll and Hill, 1952, Great Britain (72).	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 co-operating 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.	9,362 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 Denoux, 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 (98).	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							Relative risk ratio SM:NS ²	Comments
	Cases			Controls				Cases			Controls					
	Number	Percent non- smokers	Percent heavy smokers ¹	Number	Percent non- smokers	Percent heavy smokers ¹	Relative risk ratio SM:NS ²	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	5.4	(*)	(*)	(*)	(*)	(*)	(*)	...		
Schairer and Schöniger, 1943 (242).	93	3.2	31.2	270	15.9	9.3	5.7	(*)	(*)	(*)	(*)	(*)	(*)	...	16 female cases not analyzed.	
Potter and Tully, 1945 (212).	43	7.0	30.2	2,804	26.0	23.0	34.1	(*)	(*)	(*)	(*)	(*)	(*)	...		
Wassink, 1948 (304).	134	4.8	54.8	100	19.2	19.2	4.7	(*)	(*)	(*)	(*)	(*)	(*)	...	Percentages estimated from chart.	
Schrek et al., 1950 (246).	82	14.6	18.3	522	23.9	9.2	1.8	(*)	(*)	(*)	(*)	(*)	(*)	...		
Mills and Porter, 1950 (186).	444	7.2	...	430	30.5	...	5.7	(*)	(*)	(*)	(*)	(*)	(*)	...		
Levin et al., 1950 (171).	236	15.3	...	481	21.7	...	1.5	(*)	(*)	(*)	(*)	(*)	(*)	...	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							Relative risk ratio SM:NS ²	Comments
	Cases			Controls				Cases			Controls					
	Num- ber	Percent non- smokers	Percent heavy smokers ¹	Number	Percent non- smokers	Percent heavy smokers ¹	Relative risk ratio SM:NS ²	Number	Percent non- smokers	Percent heavy smokers ¹	Number	Percent non- smokers	Percent heavy smokers ¹	Relative risk ratio SM:NS ²		
Randig, 1954 (218).	415	1.2	34.2	381	5.8	17.9	75.1	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 (259).	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 under- stated. 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						Relative risk ratio SM:NS ²	Females						Relative risk ratio SM:NS ²	Comments
	Cases			Controls				Cases			Controls				
	Num- ber	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							Relative risk ratio SM:NS ²	Comments
	Cases			Controls			Relative risk ratio SM:NS ²	Cases			Controls				
	Num- ber	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	...	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 non- smokers. Heavy smokers—great- er 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	88.9	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	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).	NS 5 SM 12	<i>Po²¹⁰ levels in various tissues (pc/g tissue)</i>				Vertebral bodies, renal cortex, spleen, and urinary bladder showed no differences.	
		<i>Peribronchia!</i>	<i>Lung (average)</i>		<i>Bronchial epithelium</i>		
		<i>lymph nodes</i>			<i>negligible</i>		
		0.011	0.001-2	0.028-1.25			
		0.011	0.008				
Hill, 1965, U.S.A. (123).	NS 6 SM 4	<i>Mean Po²¹⁰ levels in various tissues (pc/kg tissue)</i>				The authors found no excessive concentrations at bronchial bifurcations.	
		<i>Bronchial tree</i>	<i>Alveolae</i>	<i>Total lung</i>	<i>Liver</i>		<i>Kidney</i>
		3.1	3.4	3.2	14.8		15.0
		7.3	9.9	2.6	20.0	20.5	
Little et al., 1965, U.S.A. (174).	NS 8 SM 25	<i>Po²¹⁰ levels in various epithelial tissue regions of lung (pc/g)†</i>				The authors noted considerable interpersonal variation but did find a trend relationship between increased daily consumption and increased <i>Po²¹⁰</i> levels in lung parenchyma. No such relationship was noted for age of individual at death or for total pack-years.	
		Site:					
		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
		<i>Mean Po²¹⁰ levels in various tissues (pc/g wet tissue)</i>			
		<i>Lung</i>	<i>Liver</i>	<i>Kidney</i>	
Ferri and Baratta, 1966, U.S.A. (95).	NS10 SM14	0.031 0.065	0.103 0.125	0.080 0.070	
		<i>Mean Po²¹⁰ levels in various tissues (pc/g)</i>			
		<i>Lung parenchyma</i>	<i>Bronchial tree</i>	<i>Bronchial bifurcation</i>	
Rajewsky and Stahlhofen, 1966, Germany (217).	NS † SM12	0.0025 0.0078	0.0020 0.0077	0.0012 0.0047	† 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.
		<i>Mean Po²¹⁰ levels in various epithelial tissues (pc/g wet tissue)</i>			
		Bronchial wall and submucosa			0.004
		Bronchial epithelium:			
		Trachea			0.120
		Lobar bronchi			0.190
		Segmental bifurcation			4.500
Little and Radford, 1967, U.S.A. (172).	SM25 Pipe 2 Ex-cigarette 1 Never 8				

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.	<i>Percent animals with:</i> <i>Treatment:</i> "Tar" alone 59.0 (81) "Tar" and croton oil 42.0 (31) Acetone alone (30) Acetone and croton oil (14)	† Number in parenthesis represents total in that experimental group. Skin-painting experiments prior to 1953 are fully detailed in tabular form in this article.
		B. 3/week for 2 years.		
		C. Whole cigarette smoke condensate in acetone.		
		Croton oil once/week.		
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.	<i>Number animals with:</i> <i>Papillomas</i> 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.	
		B. 1 or 2/week for 18 months.		
		C. 20 percent cigarette "tar" in acetone. 0.3 percent benzpyrene.		

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	
			Strain	Papillomas	Carcinomas		
Wynder et al., 1955, U.S.A. (318).	Mice of 4 separate strains.	A. Painting shaved skin.	<i>Strain</i>	<i>Papillomas</i>	<i>Carcinomas</i>	No tumors noted with acetone alone. Stresses differences in susceptibility of strain.	
		B. 3/week for 80 days.	C57BL	10/89	2/89		
		C. Whole condensate in acetone.	Swiss	22/86	12/86		
Hamer and Woodhouse, 1956, U.S.A. (116).	Outbred albino strain mice.	A. Painting unshaved skin.	<i>Treatment:</i>		<i>Papillomas</i>		
		B. Varied for 18 months.	"Tar" 2/week	1/50			
		C. Whole "tar"/acetone, benzpyrene [B(a)P], croton oil.	"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.	<i>Papillomas</i>	<i>Carcinomas</i>	(only 44/60 lived from 365-696 days).		
		B. 3/week for 2 years.	16/44	12/44			
		C. Whole "tar".					
Graham et al., 1957, U.S.A. (101).	Albino New Zealand rabbits.	A. Painting shaved skin.	<i>Treatment:</i>		<i>Papillomas</i>	<i>Carcinomas</i>	The authors review previous experiments with rabbits in tabular form.
		B. 3/week for 6 years.	Condensate	41/41	5/41		
		C. Whole condensate.	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			
Guerin and Cuzin, 1957, U.S.A. (109).	Mice (Pasteur strain.)	A. Painting neck skin.	<i>Original number</i>	<i>Survivors</i>	<i>Papillomas</i>	<i>Sarcomas</i>	† Control group.
		B. 2/week for >1 year.	†C. 112	51	0/51	0/51	‡ Experimental group.
		C. Whole condensate.	‡E. 672	220	10/220	5/220	

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	
				Number	Percent papillomas		Percent carcinomas
Wynder et al., 1957, U.S.A. (323).	Swiss mice	A. Painting skin.					
		B. Varied for 12 months.	<i>Treatment:</i>				
			5/week	50	12.0	8.0	
		C. Whole condensate in acetone.	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.	<i>Treatment CAF₁:</i>	<i>Number</i>	<i>Percent papillomas</i>	<i>Percent carcinomas</i>	Swiss mice noted to be more susceptible. Majority of carcinogens noted to be in neutral fraction of condensate.
		C. Whole "tar" or nicotine free "tar" derived from pipe and cigarette tobacco.	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	
			<i>Treatment Swiss:</i>				
			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. (39).	Paris R III mice	A. Painting shaved skin.	<i>Treatment:</i>	<i>Papillomas</i>	<i>Carcinomas</i>		
		B. Varied for 1-2 years.	Benzpyrene (twice only)	20/529	5/529		
		C. "Tar" in acetone, benzpyrene, croton oil.	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.	<i>Group:</i>	<i>Number living at 6 months</i>	<i>Percent Skin tumors at 64 weeks</i>		
		C. Whole condensate irradiation.	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.	<i>Group:</i>			Sarcomas	† Control group. ‡ Experimental group.	
			† C				1/75
			‡ E				15/75
Bock et al., 1962, U.S.A. (31).	ICR Swiss mice	A. Painting shaved skin. B. 10/week for 1 year. C. Cigarette "tar".	<i>Treatment:</i>			<i>Surviving at 18 weeks</i>	<i>Percent Skin cancer</i>	<i>Percent Skin neoplasia</i>
			Standard cigarette		24/30	25.0	54.0
			Standard cigarette		21/30	5.0	57.0
			Standard cigarette		18/30	33.0	44.0
			Standard cigarette		13/30	23.0	62.0
			Filter cigarette		30/30	7.0	27.0
			Filter cigarette		30/30	3.0	23.0
			Acetone only		66/66
Control		65/65			
Roe, 1962, U.S.A. (225).	Albino mice	A. Painting shaved skin. B. 3/week for 84 weeks. C. Whole smoke "tar" with added B(a)P in acetone.	<i>Treatment:</i>			<i>Survivors</i>	<i>Percent skin tumors</i>	Author concluded that cigarette smoke contains cocarcinogens.
			"Tar" and 0.025 mg. B(a)P		26	12.0	
			"Tar" and 0.06 mg. B(a)P		15	27.0	
			"Tar" and 0.25 mg. B(a)P		15	13.0	
			"Tar" and 1.25 mg. B(a)P		14	64.0	
B(a)P 1.25 mg.		14	...				
Druckrey and Schildbach, 1963, Germany (82).	Rats	A. Subcutaneous injection. B. 1/week for 700 days. C. Benzpyrene in tricaprylin.	<i>Treatment (BP mg./week):</i>			<i>Sarcomas</i>		
			30		25/30		
			10		14/40		
			3		8/50		
— (solvent)		2/75					

TABLE A13.—Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals (cont.)

Author, year, country, reference	Animal and strain	A. Method, B. Frequency and/or duration, C. Material	Results			Comments
			Condensate:	Complete autopsies	Percent Papillomas	
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.	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		† 7,12-dimethylbenz(a)anthracene.
			DMBA .. Ether tobacco leaf extract	Papillomas	Carcinomas	
			O .. Ether tobacco leaf extract	4/20	0/20	
			DMBA .. Chloroform tobacco leaf extract	0/20	0/20	
			O .. Chloroform tobacco leaf extract	1/20	0/20	
			DMBA .. Cigarette "tar"	0/20	0/20	
			O .. Cigarette "tar"	11/20	4/20	
			O .. Acetone	0/20	0/20	

TABLE A13.—Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals (cont.)

Author, year, country, reference	Animal and strain	A. Method B. Frequency and/or duration, C. Material	Results				Comments
Munoz et al., 1968, U.S.A. and Colombia (197).	Swiss ICR/4a mice	A. Painting shaved skin.	<i>Dark tobacco "tar"</i>	<i>At risk</i>	<i>Tumors</i>	<i>Carcinomas</i>	The authors noted a shortened latent period for dark tobacco.
		B. Varied.	4.0 percent	81	50	17	
		C. "Tar" from dark (Colombian) and light (U.S.A.) tobaccos.	8.0 percent	71	46	16	
			<i>Light tobacco tar:</i>				
			4.0 percent	95	26	6	
		8.0 percent	98	54	20		
			<i>Acetone</i>	91	0	0	
Davies and Day, 1969, Great Britain (65).	Albino mice	A. Painting shaved skin.	<i>Percent of carcinoma-bearing animals at 116 weeks</i>				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.
		B. Varied regimen.	<i>Treatment: (actual number of animals in parentheses)</i>				
		C. Cigarette and cigar condensate.	<i>300 mg.</i>	<i>150 mg.</i>	<i>75 mg.</i>	<i>37.5 mg.</i>	
		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 A.14.—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 dimethylformamide.	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 suck- ling hamster tracheas. b. Whole bron- chial 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: a. 3 mg. in olive oil b. 3 mg. in olive oil with dead Tb bacilli c. 5.75 mg. in cholesterol pellet Cigarette "tar": a. In olive oil b. In olive oil with dead Tb bacilli Controls: a. 0.15 cc. olive oil b. 0.15 cc. olive oil with dead Tb bacilli c. Cholesterol pellets	<i>Number with tumors/number exposed</i> 5/6 sarcoma. 2/4 sarcoma, 4/8 squamous cell carcinoma. 1/8 squamous cell carcinoma. 0/10. 1/8 sarcoma, 1/8 squamous cell carcinoma. 0/4. 0/4. 0/4.
Della Porta et al., 1958, U.S.A. (67).	Syrian golden hamsters.	A. Direct tracheal instillation. B. Weekly up to 45 weeks. C. 1 percent 7,12-dimethylbenz(a)anthracene (DMBA), cigarette "tar" concentrate.	Material: a. DMBA 50 μ g./week b. "Tar" 200 μ g./week c. DMBA 50 μ g./week then "tar" 200 μ g./week d. DMBA 100 μ g./week e. DMBA 100 μ g./week and "tar" 500 μ g./week Weeks	<i>Survivors at 20 weeks/original number exposed</i> 10/20 11/21 9/20 --- 7/20 9/20 <i>Number of hamsters with tracheobronchial carcinomas at death</i> 2 --- --- --- 4 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		Results					
		B. Frequency and/or duration	C. Material						
Blacklock, 1961, Great Britain (25).	CB white rats.	A. Inoculation at thoracotomy.							
		B. Once and sacrificed at 1 week-2 years.	Controls	Number of rats		Percent with malignant tumors			
		C. Cigarette tobacco smoke condensate in eucerin.	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.	Material:	Number of hamsters	Number with tumors	Number of tracheo-bronchial tumors			
		B. 0.5 cc./week for 5/6 months.	B (a) in Tween60 ...	6	3	5 (3 papillomas, 2 carcinomas).			
			B (a) P in Tween60 ¹ ..	6	3	9 (4 papillomas, 5 carcinomas).			
		C. Benzo (a) pyrene in Tween60 or olive oil.	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.	Procedure:	Number of dogs	Invasive carcinoma	Carcinoma-in situ	Pre-cancerous changes	Squamous metaplasia with atypical changes	Inflammation
			Controls	27	—	—	—	6	24
		C. Cigarette smoke condensate.	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				
			Number autopsied: Male Female	Number of tumor-bearing animals	Percent tumor- bearing of survivors at 15 weeks	Total number of tumors	Total number of respiratory tract cancers
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.	Male 23 Female 17	15 11	100.0 100.0	24 17	18 16
Kuschner, 1968, U.S.A. (157).	Hamsters.	A. Wire mesh pellet implantation into bronchus.	Implant:		Number of survivors/original number in group		Number of animals with lung cancer
		B. Lifetime.	Wire mesh only		34/35	—	
		C. B(a)P, methylcholanthrene (MCA).	MCA		88/91	43	
			B(a)P		89/91	57	
Saffiotti et al., 1968, U.S.A. (235).	Syrian golden hamsters.	A. Intratracheal inoculation.					Number of hamsters with respiratory tract tumors
		B. Weekly for 15 weeks.	Inoculate:		Number autopsied		
		C. B(a)P attached to a fine hematite dust.	Control		176	—	
			B(a)P in hematite		55	35	
			Hematite only		41	—	
Borisyuk, 1969, Russia (84).	Wistar rats.	A. Intratracheal intubation.			Number final/ initial		Duration of inoculation (months)
		B. Monthly up to 10 months.	Inoculate:				
		C. Cigarette "tar".	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.	<i>Percent of lung tumors</i> 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.	<i>Percent with alveolar carcinomas</i> 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.	<i>23 of the experimental mice showed:</i> 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.	<i>Percentage of rats with pulmonary tumors</i> 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.	<i>Number of mice</i>	<i>Number of cigarettes</i>	<i>Exposure length (months)</i>	<i>Number with severe bronchitis; peribronchitis; atypical epithelial proliferation</i>
			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.	<i>Number of mice examined</i>	<i>Exposure (days)</i>	<i>Percent of mice with pulmonary adenomatous tumors</i>	Presence of tumors showed an age-relationship independent of smoking exposure.
			81	0	56	
			39	17- 99	41	
			35	100-199	37	
			51	200-600	66	
Otto, 1963, Germany (206).	Albino mice. C. 60. E. 189.	A. Chamber. B. Approximately 12 cigarettes per day for varying intervals. C. Cigarette smoke.	<i>Number of mice examined</i>	<i>Exposure</i>	<i>Number with lung tumors</i>	
			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		
			Number of animals dead at 540 days	Daily average exposure (cigarettes)	Histologic findings in dead animals			
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.	40	1	8/ 40 MET des	MET des = desquamative metaplasia.		
			40	2	8/ 40 MET des	MET bronch = bronchial papillary metaplasia.		
			80	1-2	44/ 80 MET des (3 MET bronch, 2 PAP trach)	PAP trach = tracheal papillomata or intense tracheal metaplasia.		
			143	1-4	67/143 MET des (13 MET bronch, 8 PAP trach)			
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 transgression of lung parenchyma (percent)	
			Controls (100):				Marked squamous cell metaplasia (percent)	Marked dysplasia (percent)
			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	
			Inflam- mation	Hyperplasia with atypical features	Squamous metapla- sia with atypical features	Pre- cancerous changes	Carci- noma in situ		
Rockey and Speer, 1966, U.S.A. (223).	Mongrel dogs: C. 11. E. 19.	A. Tracheal fenestration (10). Nostril inhalation (9).						†Carcinoma <i>in situ</i> noted in 5 separate sites in this animal.	
		B. Tracheal fenestration—284 treatment days. Nostril inhalation—180 treatment days.	Controls (11) Tracheal fenestration (10) Nostril in- halation (9)	9 10 6	1 5 0	1 6 0	0 1 0		0 †1 0
		C. Cigarette smoke.							
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		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.		
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							

TABLE A16.—*Experiments concerning the effect of the inhalation of cigarette smoke or its constituents upon the respiratory tract of animals (cont.)*
(Figures in parentheses represent total number survivors in specific group)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results	Comments															
Wynder et al., 1968, U.S.A. (327).	Male C57BL6 mice: C. and E.— more than 40.	A. Chamber. B. Up to 315 cigarettes. C. Cigarette smoke, nitrogen dioxide, volatile acids and aldehydes found in cigarette smoke, swine influenza virus.	Conclusions:† No squamous cell respiratory cancer noted. This is attributed to the limitation of inhalation time (CO and nicotine acute effects) and to the anatomically and physiologically intricate nasal passage defense system. Exposure to cigarette smoke, NO ₂ , or volatile acids and aldehydes leads to reactive hyperplasia and metaplasia, both of which were noted to be reversible. Swine influenza virus exposure produced hyperplastic and metaplastic effects which could not be enhanced by subsequent exposure to cigarette smoke.	†Results not provided in tabular form.															
Laskin et al., 1970, U.S.A. (159).	Rats: C. 45. E. 3.	A. Chamber. B. 1 hour per day for up to 690 days. C. Benzo (a) pyrene aerosol, SO ₂ atmosphere (3.5 p.p.m.).	<table border="1"> <thead> <tr> <th>Exposure</th> <th>Number</th> <th>Squamous cell carcinomas</th> </tr> </thead> <tbody> <tr> <td>Atmosphere controls</td> <td>3</td> <td>0/3</td> </tr> <tr> <td>Atmosphere plus benzo (a)-pyrene exposure</td> <td>21</td> <td>2/21</td> </tr> <tr> <td>SO₂ controls</td> <td>3</td> <td>0/3</td> </tr> <tr> <td>SO₂ plus benzo (a)-pyrene exposure</td> <td>21</td> <td>5/21</td> </tr> </tbody> </table>	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	
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:	522	From same set of referrals, patients with tumors other than lip, lung, larynx-pharynx:	Random sample of 5,003 admissions; questionnaires from Hines referrals for 1942-44; records included smoking history.				
								<i>Percent</i>		<i>Percent</i>
							Nonsmokers	13.7	Nonsmokers	23.9
							Cigarettes	79.5	Cigarettes	59.2
							Cigars	3.7	Cigars	10.0
Pipes	6.8	Pipes	11.5							
Valko, 1952, Czechoslovakia (292).	M-F	226	Clinic patients with cancer of the larynx:	108	Clinic patients of same age group with other diagnoses:	Medical history and questionnaire in clinic.				
								<i>Percent</i>		<i>Percent</i>
							Nonsmokers	7.5	Nonsmokers	22.2
							Cigarettes	83.2		
							Cigars	4.4		
Pipes	10.6									
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:	615	From same set of admissions, patients with illnesses other than cancer:	Sample of 2,605 out of 2,847 interviews (including smoking history) by trained lay interviewers.				
								<i>Percent</i>		<i>Percent</i>
							Nonsmokers	4.0	Nonsmokers	13.2
							Cigarettes only	60.1	Cigarettes only	53.3
							Cigars only	2.2	Cigars only	3.4
Pipe only	4.8	Pipe only	7.0							
Some combination	28.9	Some combination	23.1							

TABLE A21.—Outline of retrospective studies of tobacco use and cancer of the larynx (cont.)

Author, year, country, reference	Sex	Number	Cases		Number	Controls		Collection of data
			Method of selection			Method of selection		
Blümlein, 1955, Germany (26).	M.	241	Clinic patients with cancer of larynx:		200	Patients with no laryngeal disease:		Personal history taken in clinic. Patients and controls over 40 years of age.
			<i>Percent</i>			<i>Percent</i>		
			Nonsmokers	0.8		Nonsmokers	18.0	
			Heavy smokers	79.3		Heavy smokers	4.3	
			Inhalers	95.0		Inhalers	17.0	
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:		209	Patients with other than epidermoid cancer, individually matched controls in same institutions:		Trained lay interviewers.
			<i>Percent</i>			<i>Percent</i>		
			Nonsmokers	0.5		Nonsmokers	10.5	
			Cigarettes	86.0		Cigarettes	73.7	
			Cigars	7.5		Cigars	10.1	
			Pipes	5.0		Pipes	3.8	
		Cigars/pipes	1.0		Cigars/pipes	1.9		
Wynder et al., 1956, India (312).	M.	132	Laryngeal cancer patients at Tata Memorial Hospital, 1952-54:		132	Controls individually matched as for U.S.A. data above:		Interviews for smoking and medical histories.
			<i>Percent</i>			<i>Percent</i>		
			Nonsmokers	13.6		Nonsmokers	30.3	
			Bidis	78.8		Bidis	62.1	
			Cigarettes	5.3		Cigarettes	4.5	
			Hookah	1.5		Hookah	0.8	
		Chilum	0.8		Chilum	2.3		
Schwartz et al., 1957, France (248).	M.	121	Patients hospitalized from 1954 through 1956 with laryngeal cancer, in Paris and other large cities:		242	Same time and sources; patients hospitalized for non-cancerous conditions or trauma:		Cases and controls individually matched within institutions; each member of a set questioned by the same trained lay interviewer.
			<i>Percent</i>			<i>Percent</i>		
			Smokers	96		Smokers (p<0.05)	84	
			Inhalers	58		Inhalers (p<0.05)	47	
			Roll their own cigarettes	44		Roll their own cigarettes	31	

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.		
			<i>Percent</i>		<i>Percent</i>				
			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.	142	Clinic patients in Havana during 1956-57, with histologically diagnosed epidermoid cancer of larynx.	220	Same source and time; apparently patients with cancers other than larynx, lung, or oral cavity, matched for age:		Interview of patients in clinic.		
	F.	32		214					
				<i>Percent</i>				<i>Percent</i>	
				<i>Male Female</i>				<i>Male Female</i>	
				Nonsmokers				1 13	Nonsmokers
		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 (88).	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.		
					<i>Percent</i>				
				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.	207	Patients admitted to chronic disease hospital during 1957 and 1958 with histologically confirmed squamous-cell carcinoma of the larynx:	912	Patients admitted during 1957 and 1958 to chronic disease center for cancerous and noncancerous conditions presumably not related to tobacco consumption:	Author interviewed patients suspected of lung cancer for smoking history and background.
	F.	13				
			<i>Percent</i>		<i>Percent</i>	
			Nonsmokers		Nonsmokers	
			Cigarettes only		Cigarettes only	
			Pipes and/or cigars		Pipes and/or cigars	
			"Heavy smokers"		"Heavy smokers"	
			Inhalers		Inhalers	
			Female smokers		Female smokers	
Rozenbils, 1967, Australia (229).	M.	191	Patients admitted to 3 major hospitals with cancer of larynx and hypopharynx:	No controls.		Patient interviews.
	F.	21				
			<i>Percent</i>			
			Nonsmokers			
			Smokers			
			Heavy smokers			
Terracol et al., 1967, France (274).	M.	961	Private service and clinic patients of ENT hospital:	No controls.		Patient interviews.
			<i>Percent</i>			
			Nonsmokers			
			Smokers			
Svoboda, 1968, Czechoslovakia (271).	M.	205	Patients admitted to a regional hospital over a period of 6 years all confirmed histologically:	320	Male controls	Cases: patient interviews. Controls: not stated.
	F.	10				
			<i>Percent</i>		<i>Percent</i>	
			Nonsmokers		Nonsmokers	
			Cigarettes		Cigarettes (approximately) ..	
			Pipes		Pipes (approximately)	

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, Czechoslovakia (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, Czechoslovakia (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	
	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent
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 <i>in situ</i>	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	
	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent
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	Controls		Comments	
		Number	Method of selection		Method of selection			
Borders, 1920, U.S.A. (43).	M.	526	Series of clinic patients with epithelioma of the lip:	500	Series of clinic patients without epithe- lioma of the lip:			
	F.	11						
			<i>Percent</i>			<i>Percent</i>		
			Tobacco users	80.5	Tobacco users	78.6		
			Smokers	75.1	Smokers	75.2		
			Cigarettes	0.9	Cigarettes	44.4		
			Chewers	24.0	Chewers	13.4		
			Pipes	59.0	Pipes	28.6		
			Cigars	38.5	Cigars	44.0		
Ebenius, 1943, Sweden (87).	M.	439	Clinic patients with cancer of the lip:	300	Not defined.		† Estimate of prevalence of use.	
	F.	33						
			<i>Percent</i>			<i>Percent</i>		
			<i>Male</i>	<i>Female</i>		<i>Male</i>	<i>Female</i>	
			Tobacco users	79.7	—	Tobacco users	68.7	—
			Tobacco users (all pipes)	—	57.6	Tobacco users	—	†1-2
			Pipes	61.8	—	Pipes	22.9	—
			Chew or use snuff	47.4	—	Chew or use snuff	60.7	—
			Cigars and cigarettes ..	12.9	—	Cigars and cigarettes ..	32.5	—
Levin et al., 1950, U.S.A. (169).	M.	143	Cancer Institute patients with cancer of the lip:	51	Cancer Institute patients with non-can- cer diseases of same site:			
			<i>Percent</i>			<i>Percent</i>		
			Smokers	84.5	Smokers	74.0		
			Cigarettes	45.3	Cigarettes	43.0		
			Pipes	48.1	Pipes	30.7		
			Cigars	26.5	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:	185	Sample of population of Columbus, Ohio, in same proportion of color, sex, and age as in cases:	
			<i>Percent</i>		<i>Percent</i>	
			Cigarettes only 35.5		Cigarettes only 32.4	
			Pipes, cigars, or combinations 54.8		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:	38	Patients of same age groups with benign oral lesions or benign surgical conditions:	
			<i>Percent</i>		<i>Percent</i>	
			Chewers 58.0		Chewers 31.6	
			Pipes 42.0		Pipes 47.4	
			Cigars and cigarettes 38.4		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:	615	Patients with illness other than cancer:	
			<i>Percent</i>		<i>Percent</i>	
			Cigarettes only 42.3		Cigarettes only 53.3	
			Cigars only 4.0		Cigars only 3.4	
			Pipes only 17.8		Pipes only 7.0	
			Mixed 28.2		Mixed 23.1	
Sanghvi et al., 1955, India (241).	M.	657	Hospital patients with cancer of oral cavity and pharynx:	288	Hospital patients with diseases other than cancer:	Smoking is of bidis among both cases and controls.
	F.	81		112		
			<i>Percent</i>		<i>Percent</i>	
			<i>Male Female</i>		<i>Male Female</i>	
			Smoke and chew 38.8 3.7		Smoke and chew 24.0 —	
			Smoke only 46.7 6.2		Smoke only 50.0 6.3	
			Chew only 11.7 64.2		Chew only 8.7 23.2	
			Neither 2.7 25.9		Neither 17.3 70.5	

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	Number	Cases		Number	Controls		Comments	
			Method of selection			Method of selection			
Ledermann, 1955, France (162).	M.	240	Patients with cancer of oral cavity and pharynx:		62	Patients with cancer of skin, bone, and muscle:		Differences between cases and controls for both high and low alcohol intake are insignificant when smoking is controlled.	
			<i>Percent</i>			<i>Percent</i>			
			Nonsmokers	4.6	Nonsmokers	17.2	>20 cigarettes per day		18.6
Wynder et al., 1957, U.S.A. (313).	M.	543	Patients with cancer of oral cavity:		207	Patients with cancer of other sites and benign diseases:			
	F.	116			232				
			<i>Percent</i>			<i>Percent</i>			
				<i>Male</i>	<i>Female</i>		<i>Male</i>		<i>Female</i>
			Nonsmokers	3	47	Nonsmokers	10		70
			Cigars	20	—	Cigars	13		—
			Pipes	11	—	Pipes	6		—
			Mixed	8	—	Mixed	8		—
			Chew	17	—	Chew	8		—
			Cigarettes	57	53	Cigarettes	63		30
		>35 cigarettes per day	29	—	>35 cigarettes per day	17	—		
		>16 cigarettes per day	—	34	>16 cigarettes per day	11		
Schwartz et al., 1957, France (248).	M.	332	Hospital patients with cancer of oral cavity and pharynx:		608	Hospital patients with non-cancer illness and accident cases, matched by age:			
			<i>Percent</i>			<i>Percent</i>			
			Nonsmokers	16.4	Cigarettes only	62.7	Pipes only		3.3
		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	Number	Cases		Number	Controls		Comments							
			Method of selection			Method of selection									
Wynder et al., 1957, Cuba (325).	M.	178	Hospital clinic patients with cancer of oral cavity and pharynx:		220	Patients in same clinics with non-malignant conditions, matched by sex and age:									
	F.	34									214				
												<i>Percent</i>		<i>Percent</i>	
												<i>Male</i>	<i>Female</i>	<i>Male</i>	<i>Female</i>
		Nonsmokers	4	24	Nonsmokers	16	66								
		Cigarettes predominantly	45	62	Cigarettes predominantly	45	27								
		Cigars predominantly	33	12	Cigars predominantly	22	6								
Wynder et al., 1957, Sweden (322).	M.	115	Male patients with cancer of oral cavity and pharynx:		115	Male patients in same hospital with cancer of sites other than oral, pharynx, larynx, lung, esophagus, breast:									
									<i>Percent</i>		<i>Percent</i>				
									<i>Cigarettes</i>	<i>13.0</i>	<i>Cigars</i>	<i>9</i>			
									<i>Pipes</i>	<i>12.2</i>	<i>Pipes</i>	<i>16</i>			
		<i>Mixed</i>	<i>15.7</i>	<i>Mixed</i>	<i>13</i>										
Peacock et al., 1960, U.S.A. (210).	M.	25	Hospital patients with oral cancer:		74	Patients in same hospital without oral cancer and 117 male and 100 female out-patients, randomly selected.									
	F.	20								72					
											<i>Percent</i>		<i>Percent</i>		
		<i>Chewed or used snuff over 20 years (all patients)</i>	<i>55.6</i>	<i>32.6 percent of first group, and 43.3 percent of second group chewed or used snuff over 20 years.</i>											
Staszewski, 1960, Poland (259).	M.	383	Male patients with oral cancer:		912	Male patients with other cancerous and non-cancerous conditions:									
									<i>Percent</i>		<i>Percent</i>				
									<i>Nonsmokers</i>	<i>5.7</i>	<i>Nonsmokers</i>	<i>17.3</i>			
									<i>"Heavy" smoking index</i>	<i>72.8</i>	<i>"Heavy" smoking index</i>	<i>49.0</i>			
									<i>Cigarettes only</i>	<i>72.3</i>	<i>Cigarettes only</i>	<i>60.5</i>			
									<i>Pipes and/or cigars</i>	<i>12.8</i>	<i>Pipes and/or cigars</i>	<i>11.1</i>			

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				
Vogler et al., 1962, U.S.A. (298).	M.	188	Clinic patients with cancer of lip and oral cavity:	521	Patients of same clinic with other cancer or non-malignant conditions:	† Due to varying tabular treatment of data, percentages of tobacco users are not all based on the same number of cases.			
	F.	92		1,064					
	Percent								
	Male Female			Percent					
							Male Female		
			Chewers						
			Excessive chewers						
			Snuff dippers						
			Excessive snuff dippers						
			Tobacco users						
				Snuff dippers					
				Tobacco users					
Vincent and Marchetta, 1963, U.S.A. (297).	M.	66	Successive patients with lesions of buccal cavity and oropharynx:	100	Successive patients attending gastrointestinal clinic, age-matched:	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.			
	F.	16		50					
	Percent								
	Oral Oro-			Percent					
	Cavity pharynx								
	Males:								
							Nonsmokers		
							<20 cigarettes per day		
							>20 cigarettes per day		
							Females:		
							Nonsmokers		
							<20 cigarettes per day		
							>20 cigarettes per day		

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					
Shanta and Krishnamurthi, 1964, India (156).	M.	552	Patients with oral and pharyngeal cancer	300	Controls residing in same area matched for age, sex, and class:					
	F.	206	(unsure of confirmation):	100						
					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.	589	Patients with oral and pharyngeal carcinoma:	589	Patients matched for age, sex, religion, and social class.					
	F.	232		232	Percent					
				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.	369	Patients with oral and pharyngeal carcinoma:	277	Patients with other (unspecified) diseases:			Found only a suggestive association between alcohol-drinking and oral cancer in non- chewers only. † BN-Betel nut.		
	F.	176		163	Percent					
				Percent	Male Female					
			Nonusers	1.6 2.5	17.0 33.0					
			Smokers	17.1 2.5	23.8 1.2					
		Smokers, †BN and tobacco chewers	46.7 6.6	24.9 1.8						

TABLE A28.—Outline of retrospective studies of tobacco use and cancer of the oral cavity (cont.)
(Data obtained from patient interview and other sources)

Author, year, country, reference	Cases			Controls		Comments		
	Sex	Number	Method of selection	Number	Method of selection			
Keller, 1967, U.S.A. (140).	M.	408	Patients with squamous cell carcinoma of oral cavity and oropharynx confirmed histologically. Three New York City VA Hospitals 1953-68:	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.		
				<i>Percent</i>			<i>Percent</i>	
				Nonusers			14.2	
				Cigarettes			56.4 (p<0.0001)	
		Pipe only	2.9					
		Cigar only	6.1					
Martinez, 1969, Puerto Rico (133).	M.	38	Patients with epidermoid carcinoma of oral cavity and pharynx:	345	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.		
	F.			114				
							<i>Percent</i>	<i>Percent</i>
							Nonsmokers	19.2
							Heavy tobacco users	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.			
				<i>Percent</i>			<i>Percent</i>	
				Nonsmokers			16.6 (p<0.001)	
				Cigarettes only			52.8	
		Pipe only	3.4					
		Pipe, other	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 (37)		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. (323)	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:	<i>Number of survivors</i>	<i>Number with benign tumors</i>	<i>Number with carcinoma</i>	
			Acetone solvent	5	1	2	
			Benzene solvent	4	—	—	
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. (182).	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:	<i>Original number</i>	<i>Surviving over 1 year</i>	<i>Number tumors</i>	<i>Inflammation and basal cell hyperplasia</i>
			Controls	30	23	..	4
			Smoke condensate	80	55	..	32
			Benz(a)pyrene	20	16	..	9
Guerin, 1959, France (108).	Strain IC and strain W rat.	A. Chamber inhalation of tobacco smoke. B. Daily (?). C. Up to 5½ months.		<i>Original number</i>	<i>Survivors</i>		<i>Buccal tumors</i>
			Controls	40	39		0/39
			Experimental	100	68		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 DMBA and MCA	<i>Original number</i> 375 71	<i>Survivors</i> 90% over 1 year 56/71 over 5-30 months	<i>Hyperplasia and/or inflammation</i> 19 —	<i>Malignant pouch tumors</i> — 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: Controls Smoke condensate DMBA			<i>Animals with lesions (time)</i> 0/18 (at 392 days). 0/20 (at 337 days) (10 showed hyperkeratosis). 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, 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 B(a)P and UV light UV light B(a)P	<i>Number</i> 40 40 40 40	<i>Duration weeks</i> 94 48 94 45	<i>Tumors</i> — — — —	

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					
			Treatment:	Original Number	Survivors	Duration	Lesions	
	Hamsters	A. Application to cheek pouch. B. See results. C. See results.	Cigarettes 5 per week	70	55	64	—	
			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. B. See results 36 weeks. 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	—	
			Concentrated Ba(OH) ₂ extract			0.5	—	
			Diluted Ba(OH) ₂ extract			0.5	—	
			None			—	—	

TABLE A29.—*Experimental studies concerning oral carcinogenesis (cont.)*

Author, year, country, reference	Animal and strain	A. Method. B. Frequency and/ or duration. C. Material.	Results												
			Original number			Percent at 13 months with									
						Papillomas	Cancer								
Protzel et al., 1964, U.S.A. (213).	Swiss Webster mice with some having liver damage in- duced either by CCl ₄ or ethyl alcohol.	A. Swabbing of labial mucosa. B. Up to 13 months. C. B(a)P in acetone.	Alcohol and CCl ₄ treated	40		74	46								
			Alcohol treated	40		84	50								
			CCl ₄ treated	40		90	40								
			No toxin	40		42	15								
Reddy and Anguli, 1967, India (219).	Swiss female mice.	A. Intravaginal instillation. B. Daily for 324-380 days. C. "Pan" mixture of areca nuts, lime, and chewing tobacco.	Original number 60	Survivors 40		Lesions 3/40 raised papillomatous malignant growths 4/40 possible carcinoma- in situ.									
Elzay, 1969, U.S.A. (80).	Syrian Golden hamsters.	A. Application to cheek pouch. B. Daily for 200 days. C. See results.	Treatment:			Original number	Mortality rate	Number animals	Percent with tumors	Percent with cancer					
			DMBA	Alcohol	Smoke						29	41.0	17	100.0	50.0
			DMBA	Alcohol						29	66.0	10	60.0	40.0
			DMBA	Smoke						29	42.0	14	100.0	70.0
			DMBA						29	48.0	15	100.0	38.0
			Alcohol	Smoke						29	42.0	14	—	—
			Smoke						29	42.0	14	—	—

TABLE A31.—*Summary of methods used in retrospective studies of tobacco use and cancer of the esophagus*

Author, year, country, reference	Cases			Controls		Collection of data
	Sex	Number	Method of selection	Number	Method of selection	
Sadowsky et al., 1953, U.S.A. (232).	M.	104	White patients admitted during 1938-48 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 questionnaire." No other details given.
Wynder et al., 1957, Sweden (222).	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.	67	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.
	F.	27				
Takano et al., 1968, Japan (272).	M.	167	Patients with esophageal cancer.	167	Patients with cancerous and non-cancerous diseases of non-digestive organs.	Interviews at various hospitals. Cases and controls age-matched.
	F.	33				

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	
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 (188).	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 15.3 14.1		—	—	3.6	—
Wynder et al., 1957, Sweden (222).	M F	13.0 (about)85.0	24.0 (about)92.0	—	—	—	—	2.1 2.0	— —
Staszewski, 1960, Poland (260).		—	18.0	95.8	59.0	87.5	80.0	—	—
Schwartz et al., 1961, France (249).		3.0	17.0	Total amount smoked daily (cigarettes) 16.8 16.0		39.0	38.0	6.6	—
Wynder and Bross, 1961, U.S.A. and India (310).	American males American females Indian males Indian females	5.0 41.0 13.0 78.0	15.0 78.0 28.0 94.0	48.0 27.0 — —	33.0 16.0 — —	— — — —	— — — —	3.4 5.1 2.6 4.5	4.4 3.2 — —
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 (189).		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	
	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent
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	Current cigarette smokers							
	Never smoked regularly		<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	109 317	Benign bladder conditions. 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. B. Another control group obtained from sample of Danish Morbidity Survey (1952, 1953, and 1954) compared with respect to smoking histories.
	F.	87		87	
Wynder, 1963, U.S.A. (326).	M.	200	First phase:	200	Admission to same hospitals (excluded cancer of respiratory system, upper alimentary tract, myocardial infarction) matched by sex and age. Same as above.
	F.	50	Admission to several hospitals in New York City during January 1957-December 1960.	50	
	M.	100	Second phase:	100	
	F.	20	Admission to same hospitals during 1961.	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 between 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	8.0	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 com- bined.
	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

	<i>Page</i>
Introduction	389
Effect on birthweight	389
Effect on outcome of pregnancy	390
Experimental studies	407
Summary	415
References	415

LIST OF TABLES

1. Summary of methods used in study of smoking and human pregnancy	391
2. Maternal smoking and infant weight	397
3. Maternal smoking and prematurity	400
4. Comparison of abortion, stillbirth, and neonatal death in smoking and nonsmoking mothers	405
5. Human experimental data on smoking and pregnancy ..	408
6. Animal experimental data on the effect of smoking and nicotine on pregnancy	411

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 non-smoking 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 per cent 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 "conception 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		Difference in mean weight of infant of smoker versus nonsmoker	Comments
	Nonsmoker	Smoker		
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	7.18 (187)	7.05 (165)	
	Female	6.74 (163)	6.67 (147)	
	Total	6.98 (350)	6.87 (312)	
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)	Cigarettes per day Infant weight
	Negro	3,173 g. (364)	3,031 g. (240)	
				White smokers:
				1-10
				11-20
				>20
				Negro smokers:
				1-10
				11-20
				>20
Murdoch (30).	7 lbs. 7.5 oz. (242)	6 lbs. 15 oz. (258)	8.5 oz.	Cigarettes per day Infant weight
				1-10
				11-20
				>20
				>40
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		Difference in mean weight of infant of smoker versus nonsmoker	Comments
	Nonsmoker	Smoker		
Zabriskie (58).	3,320 g. (1,043)	3,091 g. (957)	229 g. (8.1 oz.)	<i>Cigarettes per day</i> <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.	<i>Cigarettes per day</i> <10 121.2 (658) 116.6 (535) 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)	<i>Light smoker</i> 110.83 oz. (42) <i>Heavy smoker</i> 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)	<i>Cigarettes per day</i> <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 (86).	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)	<i>Cigarettes per day</i> 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).	118.3 oz.	<i>Cigarettes per day</i> 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 99.8 ± 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		Nonsmokers	Smokers			
Simpson (44).	<2,500 g.	Name of hospital:								Number and percent of premature infants: Nonsmokers 6.39 (328) Cigarettes per day: 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)	
		County		7.77	(144)	11.48	(96)				
		Loma Linda		6.16	(86)	12.13	(49)				
		St. Bernardines		5.21	(98)	10.50	(119)				
Lowe (28).		<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 preg- nancy 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).	No data	36 weeks	White		2.6	(10)	4.9	(21)	White .39.8	39.4	† Premature by weight but ma- ture by date (>37 weeks).
			Negro		13.7	(50)	11.3	(27)	Negro .38.8	38.8	
			†<2,500 g.		White	1.8	(7)	3.7	(16)		
		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		Percent of premature infants				Mean duration of pregnancy		Comments
	Weight	Duration of gestation	Nonsmokers	Smokers	Nonsmokers	Smokers			
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: <i>Prematurity</i> <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 Negro	3.5 (112) 4.9 (46)	6.4 (138) 13.4 (64)	(p<0.01)			Infants of smoking mothers weighed less than infants of nonsmoking mothers in each gestational age.	
	<37 weeks	White Negro	15.9 (188) 13.4 (125)	6.5 (140) 16.7 (80)				† Difference between smokers and nonsmokers not significant.	
McDonald and Lanford (26).	<2,500 g.		<i>Cigarettes per day</i>						
			4.6 (4)	<10 4.8 (2) >10 8.3 (4)					
Peterson et al. (34).	<2,500 g.		<i>Cigarettes per day</i>						
			2.5 (111)	1-10 3.0 (35) 11-20 4.8 (80) >20 3.4 (16)				Overall incidence of prematurity in smokers vs. nonsmokers significant at p<0.001.	

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	<i>Cigarettes per day</i>				
			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., (59).	<2,500 g.	Group:	<i>Cigarettes per day</i>				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 (56).	<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.		<i>Cigarettes per day</i>						Prematurity by birth weight rose directly to a significant degree ($p < 0.01$) with each smoking category. Data suggested that smoking in any trimester decreased birth weight.
			5.7 (1,417)	1-10	7.5 (571)				
				11-30	9.4 (1,358)				
	<36 weeks		5.8 (1,442)	>30	11.2 (176)				
				1-10	6.9 (525)				
				11-30	7.5 (1,084)				
			>30	7.5 (118)					
Buncher (4).								<i>Births</i> Male 39.55 weeks † 39.35 weeks Female 39.69 weeks † 39.51 weeks † Smokes 20 cigarettes per day.	
Butler and Alberman (5).	<2,500 g.		5.4 (602)		9.2 (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				2	3	4	2			5.2	7.0	10.4	4.7	
	Negro				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 (53).	2,850	2,769	250	348					87.7	125.7					
Yerushalmy (54).	White						40	30					12.4	13.9	
	Negro						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	23,629									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. ‡ Blood pressure.
	<140/90	984	496		†27	†32					†27	†65			
	=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 ($p < 0.01$) 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 <i>in vivo</i> effects of cigarette smoking on uterine activity were studied in 17 pregnant gravidas near term and not in labor. The <i>in vitro</i> 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 non-smoking 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. (15).	Chick embryo.	Chicken embryos were treated with doses of nicotine varying from 12 μ g. to 1,000 μ g. 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 : 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 the 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 pre-implantation blastocyst (blastocyst/plasma ratio ≈ 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 proportion 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.

REFERENCES

- (1) ABERNATHY, J. R., GREENBERG, B. G., WELLS, H. B., FRAZIER, T. M. Smoking as an independent variable in a multiple regression analysis upon birth weight and gestation. *American Journal of Public Health and the Nation's Health* 56 (4) : 626-633, April 1966.
- (2) BECKER, R. F., KING, J. E. Studies on nicotine absorption during pregnancy. II. The effects of acute heavy doses on mother and neonates. *American Journal of Obstetrics and Gynecology* 95 (3) : 515-522, June 15, 1966.
- (3) BECKER, R. F., LITTLE, C. R. D., KING, J. E. Experimental studies on nicotine absorption in rats during pregnancy. III. Effect of subcutaneous injection of small chronic doses upon mother, fetus, and neonate. *American Journal of Obstetrics and Gynecology* 100 (7) : 957-968, April 1, 1968.
- (4) BUNCHEER, C. R. Cigarette smoking and duration of pregnancy. *American Journal of Obstetrics and Gynecology* 103 (7) : 942-946, April 1, 1969.
- (5) BUTLER, N. R., ALBERMAN, E. D. (Editors). The effects of smoking in pregnancy. Chapter 5. IN: *Perinatal Problems*. Edinburgh, E. & S. Livingstone, Ltd., 1969. pp. 72-84.
- (6) BUTLER, N. R. A national long term study of perinatal hazards. Presented at the Sixth World Congress of Gynaecology and Obstetrics, New York, April 12-18, 1970, 11 pp.
- (7) DOWNING, G. C., CHAPMAN, W. E. Smoking and pregnancy. A statistical study of 5,659 patients. *California Medicine* 104 (3) : 187, March 1966.

- (8) DUFFUS, G. M., MACGILLEVRAI, I. The incidence of pre-eclamptic toxæmia in smokers and nonsmokers. *Lancet* 1(7550): 994-995, May 11, 1968.
- (9) ENGEL, R. R., RODKEY, F. L., O'NEAL, J. D., COLLISON, H. A. Relative affinity of human fetal hemoglobin for carbon monoxide and oxygen. *Blood* 33(1): 37-45, January 1969.
- (10) ESSENBERG, J. M., SCHWIND, J. V., PATRAS, A. R. The effects of nicotine and cigarette smoke on pregnant female albino rats and their offsprings. *Journal of Laboratory and Clinical Medicine* 25: 708-717, 1940.
- (11) FABRO, S., SIEBER, S. M. Caffeine and nicotine penetrate the pre-implantation blastocyst. *Nature* 223(5204): 410-411, July 26, 1969.
- (12) FRAZIER, T. M., DAVIS, G. H., GOLDSTEIN, H., GOLDBERG, I. D. Cigarette smoking and prematurity: A prospective study. *American Journal of Obstetrics and Gynecology* 81(5): 988-996, May 1961.
- (13) GATLING, R. R. Effect of nicotine on chick embryo. *Archives of Pathology* 78(6): 652-657, December 1964.
- (14) HADDON, W., JR., NESBITT, R. E. L., GARCIA, R. Smoking and pregnancy: Carbon monoxide in blood during gestation and at term. *Obstetrics and Gynecology* 18(3): 262-267, September 1961.
- (15) HERON, H. J. The effects of smoking during pregnancy: A review with a preview. *New Zealand Medical Journal* 61:545-548, November 1962.
- (16) HERRIOTT, A., BILLEWICZ, W. Z., HYTEN, F. E. Cigarette smoking in pregnancy. *Lancet* 1: 771-773, April 14, 1962.
- (17) KING, J. E., BECKER, R. F. Studies on nicotine absorption during pregnancy. I. LD₅₀: for pregnant and nonpregnant rats. *American Journal of Obstetrics and Gynecology* 95(4): 508-514, June 15, 1966.
- (18) KIRSCHBAUM, T. H., DILTS, P. V., JR., BRINKMAN, C. R., III. Some acute effects of smoking in sheep and their fetuses. *Obstetrics and Gynecology* 35(4): 527-536, April 1970.
- (19) KIZER, S. Influencia del habito de fumar sobre el embarazo, parto y recién nacido. (Effect of the smoking habit on pregnancy, delivery, and the newborn.) *Revista de Obstetricia y Ginecologia de Venezuela* 27(4): 595-643, 1967.
- (20) KUMAR, D., ZOURLAS, P. A. Studies on human premature births. II. *In vivo* effect of smoking and *in vitro* effect of nicotine on human uterine contractility. *American Journal of Obstetrics and Gynecology* 87(3): 413-417, October 1, 1963.
- (21) LASZLO, V. A dohányzas karos hatasai a gestatio folyamatokra. (The deleterious effects of smoking on the sequences of gestation.) *Magyar Noorvosok Lapja* 32(2): 163-167, March 1969.
- (22) LONGO, L. D. Carbon monoxide in the pregnant mother and fetus, and its exchange across the placenta. *Annals of the New York Academy of Sciences* 174(1): 313-341, October 5, 1970.
- (23) LOWE, C. R. Effect of mothers' smoking habits on birth weight of their children. *British Medical Journal* 2: 673-676, October 10, 1959.
- (24) MACMAHON, B., ALPERT, M., SALBER, E. J. Infant weight and parental smoking habits. *American Journal of Epidemiology* 82(3): 247-261, November 1963.
- (25) MANTELL, C. D. Smoking in pregnancy: The role played by carbonic anhydrase. *New Zealand Medical Journal* 63: 601-603, September 1964.

- (26) McDONALD, R. L., LANFORD, C. F. Effects of smoking on selected clinical obstetric factors. *Obstetrics and Gynecology* 26(4) : 470-475, October 1965.
- (27) MOSIER, H. D., JR., ARMSTRONG, M. K. Effect of maternal nicotine intake on fetal weight and length in rats. *Proceedings of the Society for Experimental Biology and Medicine* 124(4) : 1135-1137, April 1967.
- (28) MULCAHY, R., KNAGGS, J. F. Effect of age, parity, and cigarette smoking on outcome of pregnancy. *American Journal of Obstetrics and Gynecology* 101(6) : 844-849, July 15, 1968.
- (29) MULCAHY, R., MURPHY, J., MARTIN, F. Placental changes and maternal weight in smoking and nonsmoking mothers. *American Journal of Obstetrics and Gynecology* 106(5) : 703-704, March 1, 1970.
- (30) MURDOCH, D. E. Birth weight and smoking. *Nebraska State Medical Journal* 48(11) : 604-606, November 1963.
- (31) NEBERT, D. W., WINKER, J., GELBOIN, H. V. Aryl hydrocarbon hydroxylase activity in human placenta from cigarette smoking and nonsmoking women. *Cancer Research* 29(10) : 1763-1769, October 1969.
- (32) NISHIMURA, H., NAKAI, K. Developmental anomalies in offspring of pregnant mice treated with nicotine. *Science* 127(3303) : 877-878, April 18, 1958.
- (33) O'LANE, J. M. Some fetal effects of maternal cigarette smoking. *Obstetrics and Gynecology* 22(2) : 181-184, August 1963.
- (34) PETERSON, W. F., MORESE, K. N., KALTREIDER, D. F. Smoking and prematurity. A preliminary report based on study of 7,740 Caucasians. *Obstetrics and Gynecology* 26(6) : 775-779, December 1965.
- (35) RAVENHOLT, R. T., LEVINSKI, M. J., NELLIST, D. J., TAKENAGA, M. Effects of smoking upon reproduction. *American Journal of Obstetrics and Gynecology* 96(2) : 267-281, September 15, 1966.
- (36) REINKE, W. A., HENDERSON, M. Smoking and prematurity in the presence of other variables. *Archives of Environmental Health* 12(5) : 600-606, May 1966.
- (37) ROBINSON, P. 'Yshwn nshym Bwımmywı vzmı hırywn whshp'tw 'l h'm h'wbr whylwd. (Smoking by Burmese women during pregnancy and its influence on the mother, the fetus and the newborn.) *Harefuah* 69(2) : 37-39, 1965.
- (38) RUSSELL, C. S. Another hazard of smoking. *New Scientist* 41(631) : 64-65, January 9, 1969.
- (39) RUSSELL, C. S., TAYLOR, R., LAW, C. E. Smoking in pregnancy, maternal blood pressure, pregnancy outcome, baby weight and growth, and other related factors. A prospective study. *British Journal of Preventive and Social Medicine* 22(3) : 119-126, July 1968.
- (40) RUSSELL, C. S., TAYLOR, R., MADDISON, R. N. Some effects of smoking in pregnancy. *Journal of Obstetrics and Gynecology of the British Commonwealth* 73 : 742-746, October 1966.
- (41) SAVEL, L. E., ROTH, E. Effects of smoking in pregnancy: A continuing retrospective study. *Obstetrics and Gynecology* 20(3) : 313-316, September 1962.
- (42) SCHOENECK, F. J. Cigarette smoking in pregnancy. *New York State Journal of Medicine* 41 : 1945-1948, October 1, 1941.
- (43) SCOPPETTA, V. Sul contenuto di ossido di carbonio nel sangue circolante di gestanti fumatrici. (Carbon monoxide content in the blood circu-

- lating in pregnant smokers.) *Archivio di Ostetricia e Ginecologia* 73(3): 369-375, May-June 1968.
- (44) SIMPSON, W. J. A preliminary report on cigarette smoking and the incidence of prematurity. *American Journal of Obstetrics and Gynecology* 73(4): 808-815, April 1957.
- (45) SONTAG, L. W., WALLACE, R. F. The effect of cigarette smoking during pregnancy upon the fetal heart rate. *American Journal of Obstetrics and Gynecology* 29: 77-83, 1935.
- (46) STEELE, R., LANGWORTH, J. T. The relationship of antenatal and post-natal factors to sudden unexpected death in infancy. *Canadian Medical Association Journal* 94: 1165-1171, May 28, 1966.
- (47) TERRIS, M., GOLD, E. M. An epidemiologic study of prematurity. I. Relation to smoking, heart volume, employment, and physique. *American Journal of Obstetrics and Gynecology* 103(3): 358-370, February 1, 1969.
- (48) TJALVE, H., HANSSON, E., SCHMITTERLOW, C. G. Passage of ¹⁴C-nicotine and its metabolites into mice foetuses and placentae. *Acta Pharmacologica et Toxicologica* 26(6): 539-555, 1968.
- (49) TOKUHATA, G. K. Smoking in relation to infertility and fetal loss. *Archives of Environmental Health* 17(3): 353-359, September 1968.
- (50) UNDERWOOD, P. B., HESTER, L. L., LAFITTE, T., JR., GREGG, K. V. The relationship of smoking to the outcome of pregnancy. *American Journal of Obstetrics and Gynecology* 91(2): 270-276, January 15, 1965.
- (51) UNDERWOOD, P. B., KESLER, K. F., O'LANE, J. M., CALLAGAN, D. A. Parental smoking empirically related to pregnancy outcome. *Obstetrics and Gynecology* 29(1): 1-8, January 1967.
- (52) WELCH, R. M., HARRISON, Y. E., GOMMI, B. W., POPPERS, P. J., FINSTER, M., CONNEY, A. H. Stimulatory effect of cigarette smoking on the hydroxylation of 3,4-benzopyrene and the N-demethylation of 3-methyl-4-monomethylaminoazobenzene by enzymes in human placenta. *Clinical Pharmacology and Therapeutics* 10(1): 100-109, January-February 1969.
- (53) YERUSHALMY, J. Statistical considerations and evaluation of epidemiological evidence. IN: James, G., Rosenthal, T. (Editors). *Tobacco and Health*. Springfield, Charles C. Thomas, 1962. pp. 208-230.
- (54) YERUSHALMY, J. Mother's cigarette smoking and survival of infant. *American Journal of Obstetrics and Gynecology* 88(4): 505-518, February 15, 1964.
- (55) YOUNG, I. M., PUGH, L. G. C. E. The carbon monoxide content of foetal and maternal blood. *Journal of Obstetrics and Gynecology of the British Commonwealth* 70(4): 681-684, 1963.
- (56) YOUNOSZAI, M. K., KACIC, A., HAWORTH, J. C. Cigarette smoking during pregnancy: The effect upon the hematocrit and acid-base balance of the newborn infant. *Canadian Medical Association Journal* 99(5): 197-200, August 3, 1968.
- (57) YOUNOSZAI, M. K., PELOSO, J., HAWORTH, J. C. Fetal growth retardation in rats exposed to cigarette smoke during pregnancy. *American Journal of Obstetrics and Gynecology* 104(8): 1207-1213, August 15, 1969.
- (58) ZABRISKIE, J. R. Effect of cigarette smoking during pregnancy. Study of 2,000 cases. *Obstetrics and Gynecology* 21(4): 405-411, April 1963.

CHAPTER 6

Peptic Ulcer

Contents

	<i>Page</i>
Summary	423
References	429

LIST OF TABLES

1. Smoking and peptic ulcer disease mortality	424
2. Summary of results of retrospective and cross sectional studies of peptic ulcer and smoking	425
3. Methods used in retrospective and cross sectional studies of peptic ulcer and smoking	427

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		Mortality ratios						Comments	
			SM	NS	Cigarettes/day		Pipe		Cigar			
					Gastric	Duodenal	Gastric	Duodenal	Gastric	Duodenal		
Doll and Hill, 1964, Great Britain (5, 6).	41,000 male British physicians.	Questionnaire and follow-up of death certificate.	54	NS	†Peptic 1.00				Pipe/cigar 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 D-93 22	NS 11 SM (age 45-64) 2.95 SM (age 65-79) 4.06	1.00 (11)	1.00 (22)						
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 12 SM 25	1.00 (12)	1.00 (25)	1.00 (12)	1.00 (25)	1.00 (12)	1.00 (25)		
					All cigarette 4.13 (39)	2.98 (57)			2.84 (4)	1.59 (5)	2.90 (7)	1.58 (8)
					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)						
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 44	1.00						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.	
					All cigarette 0.53							
					± 10 1.00	0.40						
					± 20 1.67	0.59						
					≥ 30 2.38	0.32						

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

Author, year, country, reference	Sex	Number	Cases Method of selection	Controls		Comments
				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 Practitioners' 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 ulcer.	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	25.0			
	Gastric	15.0				
	Duodenal	20.0				
Trowell, 1934, England (21).	Duodenal	8.0	17.0	Average number: Cigarettes .. 12.0 per day.....11.1 per day Pipe		
				1.6 ounces per week.. 2.15 ounces per week		
Allibone and Flint, 1958, England (1).		38.0	54.0			
Doll et al., 1958, England (7).	Gastric:			Gastric: Percent smoking >25 cigarettes per day		
	Males	1.3	4.7	Males	10.6	11.3
	Females ...	51.1	66.8	Females ...	1.1	1.1
	Duodenal:			Duodenal:		
	Males	2.1	5.8	Males	10.2	12.7
	Females ...	53.7	62.0	Females ...	1.9	1.9
Edwards et al., 1959, England (8).	<i>Percent of peptic ulcer by smoking category</i>					
				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 Forsström, 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		
	Gastric	19.2		cigarettes per day		
	Not Specified ..	43.2		Age:	Gastric	Duodenal
				20	38.8	27.3
			30	45.7	43.0	47.1
			45	60.2	49.5	46.9
			60	54.1	40.4	44.0

REFERENCES

- (1) ALLIBONE, A., FLINT, F. J. Bronchitis, aspirin, smoking, and other factors in the aetiology of peptic ulcer. *Lancet* 2: 179-182, July 26, 1958.
- (2) BARNETT, C. W. Tobacco smoking as a factor in the production of peptic ulcer and gastric neurosis. *Boston Medical and Surgical Journal* 197(12): 457-459, September 22, 1927.
- (3) BATTERMAN, R. C., EHRENFELD, I. The influence of smoking upon the management of the peptic ulcer patient. *Gastroenterology* 12(4): 575-585, April 1949.
- (4) COOPER, P., KNIGHT, J. B., JR. Effect of cigarette smoking on gastric secretions of patients with duodenal ulcer. *New England Journal of Medicine* 255(1): 17-21, July 5, 1956.
- (5) DOLL, R., HILL, A. B. Mortality in relation to smoking: 10 years' observations of British doctors. Part I. *British Medical Journal* 1(5395): 1399-1410, May 30, 1964.
- (6) DOLL, R., HILL, A. B. Mortality in relation to smoking: 10 years' observations of British doctors (concluded). *British Medical Journal* 1(5396): 1460-1467, June 6, 1964.
- (7) DOLL, R., JONES, F. A., PYGOTT, F. Effect of smoking on the production and maintenance of gastric and duodenal ulcers. *Lancet* 1: 657-662, March 29, 1958.
- (8) EDWARDS, F., MCKEOWN, T., WHITFIELD, A. G. W. Association between smoking and disease in men over sixty. *Lancet* 1: 196-201, January 24, 1959.
- (9) GILLIES, M., SKYRING, A. Gastric ulcer, duodenal ulcer and gastric carcinoma: A case-control study of certain social and environmental factors. *Medical Journal of Australia* 2(25): 1132-1136, December 21, 1968.
- (10) GILLIES, M. A., SKYRING, A. Gastric and duodenal ulcer. The association between aspirin ingestion, smoking and family history of ulcer. *Medical Journal of Australia* 2(6): 280-285, August 9, 1969.
- (11) HAMMOND, E. C. Smoking in relation to the death rates of 1 million men and women. IN: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966. pp. 127-204.
- (12) KAHN, H. A. The Dorn study of smoking and mortality among U.S. veterans: Report on 8½ years of observation. IN: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966. pp. 1-125.
- (13) KASANEN, A., FORSSSTROM, J. Social stress and living habits in the etiology of peptic ulcer. *Annales Medicinae Internal Fenniae* 55(1): 13-22, 1966.
- (14) MITTY, W. F., JR., ROUSSELOT, L. M., DELANY, G. J. Smoking and its relation to nutritional status of patients following gastrectomy; a five-year follow-up survey of 171 patients. *Annals of Surgery* 150(1): 76-84, July 1959.
- (15) MONSON, R. R. Cigarette smoking and body form in peptic ulcer. *Gastroenterology* 58(3): 337-344, March 1970.

- (16) PACKARD, R. S. Smoking and the alimentary tract: A review. *Gut* 1: 171-174, 1960.
- (17) PALMER, W. L. Peptic ulcer. Chapter 32. IN: Paulson, M. (Editor). *Gastroenterologic Medicine*. Philadelphia, Lea & Febiger, 1969, pp. 710-757.
- (18) SCHNEDORF, J. G., IVY, A. C. The effect of tobacco smoking on the alimentary tract. An experimental study of man and animals. *Journal of the American Medical Association* 112(10): 898-904, March 11, 1939.
- (19) STEIGMANN, F., DOLEHIDE, R. H., KAMINSKI, L. Effects of tobacco smoking on gastric acidity and motility of hospital controls and patients with peptic ulcer. *American Journal of Gastroenterology* 22: 399-409, 1954.
- (20) THOMPSON, J. H. Effects of nicotine and tobacco smoke on gastric secretion in rats with gastric fistulas. *American Journal of Digestive Diseases* 15(3): 209-217, March 1970.
- (21) TROWELL, O. A. The relation of tobacco smoking to the incidence of chronic duodenal ulcer. *Lancet* 1: 808-809, April 14, 1934.
- (22) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. *Vital Statistics of the United States—1967. Vol. II—Mortality, Part A*. Washington, U.S. Department of Health, Education and Welfare, Public Health Service Publication, 1969.
- (23) WEIR, J. M., DUNN, J. E., JR. Smoking and mortality: A prospective study. *Cancer* 25(1): 105-112, January 1970.

CHAPTER 7

Tobacco Amblyopia

Contents

	<i>Page</i>
Summary and conclusions	436
References	436

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 B₁₂, 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.

REFERENCES

- (1) CANADIAN MEDICAL ASSOCIATION JOURNAL. Tobacco amblyopia. (Editorial) Canadian Medical Association Journal 102(4) : 420, February 28, 1970.
- (2) CHISHOLM, I. A., BRONTE-STEWART, J., FOULDS, W. S. Hydroxocobalamin versus cyanocobalamin in the treatment of tobacco amblyopia. Lancet 2(7513) : 450-451, August 26, 1967.
- (3) DARBY, P. W., WILSON, J. Cyanide, smoking, and tobacco amblyopia. Observations on the cyanide content of tobacco smoke. British Journal of Ophthalmology 51(5) : 336-338, May 1967.
- (4) DREYFUS, P. M. Blood transketolase levels in tobacco-alcohol amblyopia. Archives of Ophthalmology 74(5) : 617-620, November 1965.
- (5) DUNPHY, E. B. Alcohol and tobacco amblyopia: A historical survey. American Journal of Ophthalmology 68(4) : 569-578, October 1969.
- (6) FOULDS, W. S., BRONTE-STEWART, J. M., CHISHOLM, I. A. Serum thiocyanate concentrations in tobacco amblyopia. Nature 218(5141) : 586, May 11, 1968.
- (7) FOULDS, W. S., CANT, J. S., CHISHOLM, I. A., BRONTE-STEWART, J., WILSON, J. Hydroxocobalamin in the treatment of Leber's hereditary optic atrophy. Lancet 1(7548) : 896-897, April 27, 1968.
- (8) FOULDS, W. S., CHISHOLM, I. A., BRONTE-STEWART, J., WILSON, T. M. Vitamin B₁₂ absorption in tobacco amblyopia. British Journal of Ophthalmology 53(6) : 393-397, June 1969.
- (9) FOULDS, W. S., CHISHOLM, I. A., BRONTE-STEWART, J., WILSON, T. M. The optic neuropathy of pernicious anemia. Archives of Ophthalmology 82(4) : 427-432, October 1969.
- (10) FREEMAN, A. G., HEATON, J. M. The aetiology of retrobulbar neuritis in Addisonian pernicious anaemia. Lancet 1(7183) : 908-911, April 29, 1961.

- (11) HEATON, J. M., MCCORMICK, A. J. A., FREEMAN, A. G. Tobacco amblyopia: A clinical manifestation of vitamin-B₁₂ deficiency. *Lancet* 2(7041): 286-290, August 9, 1958.
- (12) KNOX, D. L. Neuro-ophthalmology. *Archives of Ophthalmology* 83(1): 103-127, January 1970.
- (13) LINDSTRAND, K., WILSON, J., MATTHEWS, D. M. Chromatography and microbiological assay of vitamin B₁₂ in smokers. *British Medical Journal* 2 (5520): 988-990, October 22, 1966.
- (14) LINNELL, J. C., SMITH, A. D. M., SMITH, C. L., WILSON, J., MATTHEWS, D. M. Effects of smoking on metabolism and excretion of vitamin B₁₂. *British Medical Journal* 2(5599): 215-216, April 27, 1968.
- (15) SCHEPENS, C. L. Is tobacco amblyopia a deficiency disease- Transactions of the Ophthalmological Society of the United Kingdom 66: 309-331, 1946.
- (16) SCHIEVELBEIN, H., WERLE, E., SCHULZ, E. K., BAUMEISTER, R. The influence of tobacco smoke and nicotine on thiocyanate metabolism. *Naunyn-Schmiedebergs Archiv für Pharmakologie und Experimentelle Pathologie* 262(3): 358-365, February 5, 1969.
- (17) SILVETTE, H., HAAG, H. B., LARSON, P. S. Tobacco amblyopia. The evolution and natural history of a "tobaccogenic" disease. *American Journal of Ophthalmology* 50(1): 71-100, January 1960.
- (18) SMITH, A. D. M. Retrobulbar neuritis in Addisonian pernicious anaemia. (Letter) *Lancet* 1(7184): 1001-1002, May 6, 1961.
- (19) SMITH, A. D. M., DUCKETT, S. Cyanide, vitamin B₁₂, experimental demyelination and tobacco amblyopia. *British Journal of Experimental Pathology* 46(6): 615-622, December 1965.
- (20) TRAQUAIR, H. M. Toxic amblyopia, including retrobulbar neuritis. Transactions of the Ophthalmological Society of the United Kingdom 50: 351-385, 1930.
- (21) VICTOR, M. Tobacco-alcohol amblyopia. A critique of current concepts of this disorder, with special reference to the role of nutritional deficiency in its causation. *Archives of Ophthalmology* 70(3): 313-318, September 1963.
- (22) VICTOR, M. Tobacco amblyopia, cyanide poisoning and vitamin B₁₂ deficiency. A critique of current concepts. Chapter 3. IN: Smith, J. L. (Editor) *Neuro-Ophthalmology*. Symposium of the University of Miami and the Bascom Palmer Eye Institute. Hallandale, Florida, Huffman Publishing Co., 1970. pp. 33-48.
- (23) WALSH, F. B., HOYT, W. F. (Editors) Neurotoxic substances affecting the visual and ocular motor systems. Chapter 15: IN: *Clinical Neuro-Ophthalmology*, Volume 3, 3rd Edition. Baltimore, The Williams & Wilkins Company, 1969. pp. 2613-2616.
- (24) WATSON-WILLIAMS, E. J., BOTTOMLEY, A. C., AINLEY, R. G., PHILLIPS, C. I. Absorption of vitamin B₁₂ in tobacco amblyopia. *British Journal of Ophthalmology* 53(8): 549-552, August 1969.
- (25) WILSON, J. Leber's hereditary optic atrophy: A possible defect of cyanide metabolism. *Clinical Science* 29(3): 505-515, December 1965.
- (26) WILSON, J., MATTHEWS, D. M. Metabolic inter-relationships between cyanide, thiocyanate and vitamin B₁₂ in smokers and nonsmokers. *Clinical Science* 31(1): 1-7, January 1966.

- (27) WOKES, F., PICARD, C. W. The role of vitamin B₁₂ in human nutrition. *Clinical Nutrition* 3(5) : 383-390, September-October 1955.
- (28) WYNDER, E. L., HOFFMANN, D. Certain constituents of tobacco products. Chapter 8. K. Vapor phase of tobacco smoke. IN: Wynder, E. L., Hoffmann, D. (Editors). *Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis*. New York, Academic Press, 1967. pp. 451-453.

Index

- Abortions
 smoking effects on, 13
- Abortions, spontaneous
 comparison of stillbirth and neonatal death with, in smoking and nonsmoking mothers, 390, 405-406
- Acidosis
 metabolic, smoking mother effects on infant, 407
- Adenocarcinoma
 prevalence in male and female smokers and nonsmokers, 250
 relationship of cigarette smoking to, 246-249, 296
- Adenoma
 papillary, induction in rats by exposure to cigarette tars, 348
 pulmonary, induction in mice by cigarette smoke inhalation, 349
 renal, relationship of smoking to, 296
- Adrenal gland
 catecholamine release from, nicotine effects on, 36
- Advisory Committee on Smoking and Health
 establishment and conclusions of study by, 3
 report on cigarette smoke and condensates effects on oral cavity of animals, 288
- Age
 atypical nuclei in esophageal epithelium arranged by smoking and, 379-380
 current cigarette smokers by sex and, 6
 effects on CHD, 27, 39
- AHA
 see American Heart Association
- Air pollution
 as cause of COPD, 152, 216-217
 effect on COPD development, 175
 relationship of lung neoplasms, smoking and place of residence, 252-255
 role in etiology of lung cancer, 11, 276
- Alcohol
 effect of consumption on esophageal neoplasms in smokers, 289, 293
 effect of consumption on laryngeal neoplasms among tobacco users, 280
 effect of consumption on tobacco amblyopia 435-436
 effect of heavy consumption and heavy smoking on oral neoplasms, 288
 ethanol, penetrability of dissolved benzo(a)pyrene in mice esophageal epithelium, 293
 relationship of smoking and, in human tuberculosis, 172
- Alcoholism
 patients with, smoking and ventilatory function in, 213
- Amblyopia
 characterization of, 435
 development from cyanide component of tobacco smoke, 14
 incidence of, 435
- American Heart Association
 pooling project on CHD, 23, 28, 30, 39
- Aminoazo dyes
 activity in placenta of smoking mothers, 410
- Angina pectoris
 cause of, 21
 incidence with cigarette smoking, 24, 37
 in Danish twins, smokers vs. nonsmokers, 51
 in twins, constitutional factors, 50-51
 prospective studies of, CHD morbidity relation to smoking 37, 39
- Animals
 see also specific animals e.g., cats, dogs, rabbits, etc.
 atherosclerotic lesion development in, smoking enhancement, 36
 carcinoma induction in, from arsenic, 257
 cigarette smoke effect on pulmonary physiology and structure in, 162
 development of lesions from cigarette smoke inhalation, 11
 effects of nicotine on cardiovascular system of, 57, 107-112
 esophageal neoplasms in, induction by nitrosamines, 292
 respiratory tract of, neoplastic changes following cigarette smoke inhalation, 238-239
 skin of, carcinogenicity of tobacco tars, 238, 267
 tests of, with smoke carcinogens, 12
 ventilatory function change from smoking, 10
- Anti-trypsin, alpha₁
 COPD predisposition from genetic absence of, 150
 determination using immunoelectrophoresis, 151
 relationship in pulmonary emphysema, 10-11
- Anthranilic acid, 3-hydroxy-
 urinary excretion of, smoking effects on, 296
- Aorta
 aneurysms of, cigarette smoking effect on, 9, 67, 71, 75
 atherosclerosis in, long term smoking effects, 52-56
- Areca nut
 see Betel nut
- Aromatic compounds
 carcinogenic properties in cigarette

- smoke from, 264, 265
- detection in urine using chemiluminescence technique, 297
- stimulation of placental BP-hydroxylase activity in pregnant rats by, 414
- Arrhythmia**
 - formation in nicotine stimulated damaged myocardium, 58
- Arsenic**
 - lung neoplasm mortality in smelter workers exposed to, 257
 - respiratory tract carcinoma in workers exposed to, 256, 257
- Arteries**
 - aneurysm in aortic, cigarette smoking effects on, 9, 67, 71, 75
 - atherosclerotic, increased by cigarette smoking, 8, 63
 - flow of carotid, cigarette smoking effects on, 67
 - hypoxemia, development from cigarette smoking, 9
 - occlusions of, cigarette smoking effects on, 73
 - walls of, mechanism of lipoprotein infiltration, 63
 - walls of nicotine-induced necrosis, 63
- Arteriosclerosis**
 - see also* Thromboangiitis obliterans
 - in aorta and coronary arteries, cigarette smoking effects on, 45, 52-56
 - cigarette smoking effects on, 8
 - development by increased carboxyhemoglobin formation, 9
 - development of, carbon monoxide effects on, 63
 - development of, effects of nicotine on, 38
 - lesion development in, smoking enhancement, 36
 - peripheral, cigarette smoking effects on, 72-73
- Arteriosclerotic heart disease (ASHD)**
 - see* Coronary disease
- Asbestos workers**
 - see* Occupations
- ASHD**
 - see* Coronary disease
- Asia**
 - see also* specific countries of Asia
 - Central and Southeast, relationship of tobacco use and neoplasms of oral cavity, 366
- Asthma**
 - bronchial, cigarette smoking effects on, 10, 175
- Atherosclerosis**
 - see* Arteriosclerosis
- Atropine**
 - effects on bronchoconstriction in dogs, 163
- Australia**
 - COPD morbidity in smokers in, 203
 - laryngeal neoplasms in, relationship to tobacco use, 357
 - lung neoplasm in, retrospective studies of, 327
 - peptic ulcer in, methods for retrospective and cross-section studies of smoking and, 426, 428
- Bacteria**
 - effect of cigarette smoke on action of macrophages on, 165
 - pneumonia, mice resistance following cigarette inhalation, 173
- Bank employees**
 - see* Occupations
- Benz(e)acephenanthrylene**
 - carcinogenic properties in cigarette smoke from, 264, 265
- Benz(a)anthracene**
 - alcoholic solution of, penetrability of mice esophageal epithelium, 292
- Benz(a)anthracene, 7,12-dimethyl**
 - carcinoma induction in hamsters following instillation of, 346
 - skin painting with, papilloma and carcinoma induction in mice by, 341
- Benzo(b)fluoranthene**
 - see* Benz(e)acephenanthrylene
- Benzo(j)fluoroanthene**
 - carcinogenic properties in cigarette smoke from, 265
- Benzo(c)phenanthrene**
 - carcinogenic properties in cigarette smoke from, 265
- Benzo(kt)pentaphene**
 - carcinogenic properties in cigarette smoke from, 265
- 3,4-Benzopyrene**
 - see* Benzo(a)pyrene
- Benzo(a)pyrene**
 - ability of smoking mothers to hydroxylate, 407
 - alcoholic solution of, penetration of mice esophageal epithelium, 292
 - carcinogenicity of, in relation to asbestos in hamsters, 257
 - carcinogenic properties in cigarette smoke from, 264, 265
 - detoxification by lung aryl hydroxylase, 257
 - effects of instillation or implantation in animal tracheobronchial tree, 346-347
 - effects on animal tissue and organ cultures in, 343-345
 - effects with influenza virus on cigarette inhalation by mice, 352
 - sarcoma induction in rats following instillation of, 346
 - skin painting with, papilloma induction in mice by, 337-338
- Benzo(a)pyrene, 1-methyl-**
 - carcinogenic properties in cigarette smoke from, 265
- Betel nut**
 - chewers of, relationship with oral cavity neoplasms, 366, 369-370
- Birth weight**
 - see* Neonate
- Blacks**
 - maternal smoking and infant weight, 397
 - maternal smoking and prematurity, 400-401
- Bladder neoplasms**
 - frequency in smokers vs. nonsmokers, 238, 293-295
 - methods of retrospective studies of smoking and, 293, 381-384
 - presence of tryptophan metabolites in

- urine of patients with, 296-297
- relationship of cigarette smoking to, 299
- urinary, cigarette smoking relationship, 13
- U.S. mortality in 1967, 294
- Blood**
 - see also specific components of blood, e.g., cholesterol, lipids, platelets
 - carboxyhemoglobin formation in, from smoking, 60, 75
 - clotting, cigarette smoking effects on, 9, 36
- Blood circulation, coronary**
 - alteration following cigarette smoke inhalation, 58
 - effect of variations in hemoglobin and hematocrit, 66
- Blood pressure**
 - diastolic, cigarette smoking effects, 8, 23
 - diastolic, in smokers with CHD, 21-22, 24, 42
 - high, risk factor in arteriosclerosis obliterans, 72
 - high, risk in mortality from CVD, 67
 - hypertensive vs. non-hypertensive, mortality rates of CHD in, 42
 - nicotine effects on, 36
 - relationship of smoking and CHD, 43, 47
 - smokers vs. nonsmokers, 41, 42, 103-104
 - systolic, mortality from elevated, with CHD, 42
- BP-hydroxylase**
 - see under Enzymes
- Bradycardia**
 - development in dogs given nicotine, 57
- British Perinatal Mortality Survey**
 - results of, 390
- Bronchitis, chronic**
 - cigarette smoking cause and effect relationship, 3, 9
 - definition, 139
 - mortality in cigarette smokers, 175
 - mortality rates in 1967, 139
 - smokers vs. nonsmokers, 195-205
- Bronchogenic carcinoma**
 - see Carcinoma, bronchogenic
- Bronchopneumonia**
 - development in dogs following cigarette smoke inhalation, 271
- Bronchopulmonary disease, chronic obstructive**
 - see also Asthma, bronchitis, emphysema, respiratory diseases
 - air pollution relationship in, 152, 216-217
 - characterization of, 139
 - cigarette smoking effects on development, 4, 9-11, 175
 - effect of smoking cessation on development, 10
 - genetic factors in pathogenesis of, 148, 150-152, 205
 - increased prevalence of heterozygotes in, 151-152
 - mortality in pipe, cigar, and cigarette smokers, 175
 - mortality rates from, 139-145
 - smoking effects on ventilation-perfusion measurements in, 163
- Buerger's disease**
 - see Thromboangiitis obliterans
- Burma**
 - methods used in smoking study and human pregnancy, 393
- Butylamine, N-methyl-nitroso**
 - suspected carcinogenic properties in cigarette smoke from, 265
- Cadmium**
 - in cigarette smoke, relation to emphysema pathogenesis, 154
- Calves**
 - see Cattle
- Canada**
 - COPD morbidity of smokers in, 204
 - human experimental data on smoking and pregnancy, 409
 - infectious respiratory disease in, relationship to smoking, 228
 - kidney and bladder neoplasms in smokers in, 294
 - mortality rates from COPD, 139-141, 145
 - mortality ratios from COPD, 143
 - mortality ratios in smokers and nonsmokers from pancreatic neoplasms, 298
 - thrombosis in, smoking relationship, 132
 - veterans of, lung neoplasm mortality ratios in smokers and nonsmokers, 241
- Carbazole, 9-methyl-**
 - possible importance in tobacco carcinogenesis, 266
- Carbon-14**
 - labeled smoke particulate deposition in hamster respiratory tract, 281-282
- Carbonic anhydrase**
 - see Enzymes
- Carbon monoxide**
 - in cigarette smoke, formation of carboxyhemoglobin, 8-9
 - effects on cholesterol-fed rabbits, 65-66
 - effects on human physiology, 60-62
 - levels in cigarette smoke, 59
 - levels in fetal blood of smoking mothers, 407-410
- Carboxyhemoglobin**
 - effects of elevated, on fetal tissues, 407
 - formation in blood of smokers, 60, 75
 - formation from CO in cigarette smoke, 8-9
- Carcinogens**
 - action on oral cavity, effect of saliva, 288
 - listing of, in cigarette smoke, 265-266
 - in smoke, effect on oral cavity, 12
- Carcinoid**
 - prevalence in male and female smokers and nonsmokers, 250
- Carcinoma**
 - formation following animal skin painting with smoke condensates, 337-342
 - induction in rats exposed to cigarette tars, 348
 - undifferential, relationship to cigarette smoking, 248-249
- Carcinoma, alveolar**
 - induction in mice by cigarette smoke inhalation, 349

- Carcinoma, anaplastic
 - prevalence in male and female smokers and nonsmokers, 250
- Carcinoma, bronchogenic
 - development in dogs following cigarette smoke inhalation, 269, 272-273
 - mortality from, relationships to smoking, air pollution and residence, 253
 - mortality in smokers vs. nonsmokers asbestos workers, 257
- Carcinoma, epidermoid
 - mortality from, relationship to smoking, air pollution and residence, 254
 - prevalence in male and female smokers and nonsmokers, 250
 - relationship of cigarette smoking to, 246-249
- Carcinoma, epithelial
 - induction in mice by cigarette smoke inhalation, 350
- Carcinoma, oat cell
 - relationship of cigarette smoking to, 247
- Carcinoma, squamous cell
 - development in mice drinking alcoholic benzo(a)pyrene, 292
 - in oral cavity, relationship to tobacco use, 366-367
- Carcinoma, tracheobronchial
 - induction in hamsters by cigarette smoke instillation, 346-347
- Cardiovascular diseases
 - see also* Coronary disease
 - atherosclerotic, cigarette smoking relationship, 4
- Cardiovascular system
 - nicotine and cigarette smoke effects on, 56-58, 107-118
- Catecholamines
 - adrenal gland release, effect of nicotine on, 36
 - effect on blood flow in coronary arteries, 58
 - release by cigarette smoking, 8
 - release in animals by nicotine, 57, 119
- Cats
 - cardiovascular function in, smoking and nicotine effects on, 110, 111
 - ciliary function in, effect of cigarette smoke on, 222-224
 - lungs of, cigarette smoke effect on surfactant activity, 225
- Cattle
 - ciliary function in, effect of cigarette smoke on, 221
- CBF
 - see* Blood circulation coronary
- Central nervous system
 - effects of carbon monoxide in smoke on, 60
- Cerebrovascular disease
 - definition of, 66
 - mortality from, effects of cigarette smoking on, 9
 - mortality rates from, smokers vs. nonsmokers, 66-70
- Cessation of smoking
 - effect on COPD development in British physicians, 142
 - effect on COPD morbidity in smokers vs. nonsmokers, 146
 - effect on development of COPD, 140
- effect on mortality from COPD from, 175
- improvements in respiratory system, 148, 149
- relation to incidence and mortality from CHD, 32, 46-48, 106
- CHD
 - see* Coronary disease
- Chemiluminescence
 - see* Luminescence
- Chewing
 - see* Betel nut and tobacco
- Chickens
 - ciliary function in, effect of cigarette smoke on, 223
 - embryos of, effect of cigarette smoke on, 344
 - embryo of, nicotine effects on CNS, 411
- Chile
 - atherosclerosis autopsy studies in, 55
 - atherosclerosis in, no smoking effect found, 56
- Cholesterol
 - rabbits fed, carbon monoxide effects on, 65-66
 - serum, cigarette smoking relationship with, 8
 - serum, control in coronary disease, 21-22
 - serum, relationship of cigarette smoking to levels of, 41, 43
 - serum, relationship of elevated with cigarette smoking in peripheral vascular disease, 72
 - serum, in smokers vs. nonsmokers, 41, 98-102
 - serum, in smokers with CHD, 23-24, 43
 - synergistic relationship of carbon monoxide in coronary atheromatosis, 63
- Chromium
 - respiratory tract carcinoma in workers exposed to, 256
- Chromium compounds
 - lung neoplasm mortality from, 257-258
- Chronic obstructive pulmonary disease
 - see* Bronchopulmonary disease, chronic obstructive
- Chrysene
 - carcinogenic properties in cigarette smoke from, 265
- Chrysene, 1-methyl-
 - carcinogenic properties in cigarette smoke from, 265
- Cigarette filters
 - advantages in reduction of particulates, 269, 275
 - reduction of lung neoplasms from, 13
- Cigarette smoke
 - alteration of coronary blood flow, 58
 - bronchogenic carcinoma induction in dogs inhaling, 269, 270
 - cadmium levels in, 154
 - carbon monoxide levels in, 59
 - carcinogenicity of components to animals, 12, 277
 - cause of death in dogs from inhalation, 271
 - ciliary movement inhibition, 267
 - effect on tissue and organ cultures, 267, 343-345

effect of nickel on induction of lung aryl hydroxylase, 256-257
 high tar, risks in, 11
 inhalation by dogs, lung neoplasm development, 268-269, 272-274
 inhalation effects on animal respiratory tract, 268-269, 349-353
 inhalation effects on hamster larynx, 281, 284
 listing of identified or suspected tumorigenic agents, 264-267
 2-naphthylamine identified in, 265
 neoplastic changes in animals inhaling, 238-239
 tobacco amblyopia relationship to cyanide metabolism in, 435-436
Cigarette smoke condensates
 carcinogenic effect on animal oral cavities, 288
 carcinogenic properties on animal skin, 337-342
 effects of instillation or implantation in animal tracheobronchial tree, 346-348
 effects on tissue and organ cultures, 343-344
 painting skin of animals with, 337-342
Cigarette smokers
 arterial occlusions in, 73
 atherosclerosis in aortic and coronary arteries, 52-56
 atypical nuclei in male esophageal epithelium, 379-380
 bladder neoplasms in, 293-295
 cell rows and atypical cells in vocal cords of, 280, 359-360
 cessation effects on COPD morbidity, 146, 197, 199, 203-204
 cessation lowers lung neoplasm rate in, 11
 changes in ventilatory function and pulmonary histology, 175
 CHD in AHA pooling project, 28, 30, 39
 CHD risk by, 23-25
 comparative risk for lung neoplasms, 237
 decline in British physicians, 48
 development of altered ventilatory function in young, 10
 development of esophageal neoplasms, 12, 293
 development of laryngeal neoplasms, 12
 development of oral neoplasms, 12
 development of second primary oral neoplasms in continuing, 287
 effect of filters on emphysema development, 162
 effects of inhalation on bronchial reactivity, 164
 effect on cardiovascular system, 56-58, 107-118
 effects on uterine activity in gravidic women, 408
 esophageal neoplasm mortality ratios in, 290-291
 etiological cause of lung neoplasms, 239
 histology and smoking relationship of lung neoplasms in 246-249
 infant birth weight, 397-399
 inhalation effects on human pulmonary function, 163, 166-169
 kidney neoplasms in, 294-296
 laryngeal neoplasm induction in, 354-357
 lung neoplasm mortality in, 240, 243-244
 mortality from cerebrovascular disease, 67-70
 mortality rates affected by sex, 3
 mortality ratios from COPD, 142-144
 mortality ratios from pancreatic neoplasms in, 298
 mortality ratios from peptic ulcers in, 424
 peptic ulcer in, smoke effects on antacid therapy, 423
 percentage of women of child-bearing age, 389
 possible processes for increased mortality in, 4-5
 postoperative pulmonary complications in, 174, 230
 pulmonary surfactant activity in, 172, 225
 relationship of asbestos in lung neoplasm mortality, 257
 relationship in coronary and lower limb arteriosclerosis, 72
 relationship of former to lung neoplasm development, 276
 relationship to infectious respiratory disease, 172, 226-229
 relationship to laryngeal neoplasm development in, 281
 relationship to lip or oral cavity neoplasms, 361-370
 relationship to lung neoplasms, 275
 relationship with bladder neoplasms in men, 299
 relationship with dust on COPD development, 153
 with peptic ulcer, 427
 risk in CHD, 8
 risk of COPD in, 140
 survey by age and sex, 6
 survey of U.S., 6
Cigarettes
 development of esophageal neoplasms by, 12, 293
 tar levels of, relationship to lung neoplasm development, 276
Cigar smokers
 atypical nuclei in male esophageal epithelium, 379
 bladders neoplasms in, 293-294
 cell rows and atypical cells in vocal cords of, 280, 359-360
 COPD morbidity in, 146, 197-198, 201-202, 204-205
 effects of smoke on bronchial reactivity, 164
 esophageal neoplasm mortality ratios in, 290
 kidney neoplasms in, 294-295
 lack of risk in CVD, 67
 laryngeal neoplasm induction in, 12, 354-357
 lung neoplasm incidence in rural Switzerland, 244
 lung neoplasm mortality in, 11, 240-243
 mortality ratios from COPD in, 142-143, 145

- myocardial infarction in, 32, 38-39
- relationship to infectious respiratory disease, 227
- relationship of laryngeal neoplasms development in, 281
- relationship of neoplasms of oral cavity with, 12, 361-365, 367-371
- mortality ratios from pancreatic neoplasms in, 298
- mortality ratios from peptic ulcer in, 424
- risk of CHD, 8
- risk of COPD, 10
- risk of lung neoplasm development, 276
- Ciliary activity
 - see Respiratory system
- Circulation
 - see Blood circulation
- Cirrheses
 - see Liver
- Civil servants
 - see Government employees under Occupations
- Coal miners
 - see Occupations
- Congressional legislation
 - see Laws
- Connecticut Cancer Registry
 - figures on age-adjusted larynx neoplasm incidence, 277
 - figures on incidence of oral neoplasms, 284
- Constitutional hypothesis
 - relationship to CHD and smoking, 48-49, 105-106
- COPD
 - see Bronchopulmonary disease, chronic obstructive
- Corn silk
 - smoking, lack of arterial epinephrine level increase, 57
- Coronary blood flow
 - see Blood circulation, coronary
- Coronary disease
 - see also Angina pectoris
 - age-adjusted rates in smokers, 23
 - arteriosclerotic, mortality rates in U.S., 21
 - atherosclerosis in, effects of smoking on, 4, 63
 - blood pressure of smokers vs. nonsmokers, 43, 47
 - carbon dioxide effects on oxygen uptake in, 62
 - cigarette smoking relationship, 5
 - death ratios of paired combinations of high risk, 25
 - first, mortality rates in smokers vs. nonsmokers, 24, 26-29
 - incidence and mortality rates in former smokers, 46, 47-48
 - infarction in NYC pipe and cigar smokers, 32, 38-39
 - infarction relationship to physical activity, smokers vs. nonsmokers, 44
 - in smokers with predisposing factors, 24
 - morbidity relationship of smoking to, 32-35, 37, 39, 93-97
 - mortality and morbidity retrospective studies, 40, 93-97
 - mortality from, relationship to electrocardiographic findings, 42
 - mortality in obese vs. non-obese, 45
 - mortality rates in, hypertensives vs. non-hypertensives, 42
 - mortality rates in, smokers vs. nonsmokers, 21-22
 - mortality rates in, with increased carbon monoxide, 62
 - mortality rates of paired combinations of high risk, 25
 - mortality rates of cigarette smokers from, AHA pooling project, 28, 30, 39
 - mortality rates of U.S. veterans, 26, 38
 - myocardial infarction in Danish twins, 51
 - nicotine effect on coronary blood flow in, 58
 - relation of triglycerides to, 65
 - relationship of blood pressure and smoking, 45, 47
 - relationship of heart rate and smoking, 45, 47
 - relationship of physical activity and smoking, 41, 43, 44
 - relationship to constitutional makeup and smoking, 48-49, 105-106
 - relationship to ECG abnormalities and smoking, 45, 47
 - relationship to obesity and smoking, 43-45
 - risk factors, 23-24, 40-41
 - smokers age effects on development, 27, 39
 - smoking risk factor, 8
 - sudden mortality in, smoking effects on, 52
- Coronary heart disease
 - See Coronary disease
- Cows
 - see Cattle
- Cresol
 - suspected carcinogenic agent of cigarette smoke, 266
- Cuba
 - laryngeal neoplasms in, relationship to tobacco use, 356
 - relationship of tobacco use and neoplasms of oral cavity, 364
- CVD
 - see Cerebrovascular disease
- Cyanides
 - metabolism of, pathogenesis of tobacco amblyopia relationship to, 435-436
 - in tobacco amblyopia etiology, 14
- Czechoslovakia
 - laryngeal neoplasms in, relationship to tobacco use, 354, 357
 - serum lipid difference in smokers vs. nonsmokers in, 101
- Death rates
 - see Mortality rates
- Denmark
 - atherogenic effect of carbon monoxide and hypoxia, 64
 - bladder neoplasms in, methods and results in retrospective studies of smoking and, 381, 383
 - carbon monoxide effects on human blood lipids in, 129

carbon monoxide effects on rabbit blood lipids in, 129
 serum lipid differences in smokers vs. nonsmokers in, 102
 twins in, angina pectoris in smokers vs. nonsmokers, 51

Deoxyribonucleic acid
 content increase in smokers oral epithelial cells, 288
 levels in mice lung exposed to cigarette smoke, 161

Diabetes
 effect on CHD in smokers, 24
 risk in mortality from CVD, 67

Diabetes mellitus
 relationship with cigarette smoking in peripheral vascular disease, 72

Dibenz(*a,h*)acridine
 carcinogenic properties in cigarette smoke from, 265

Dibenz(*a,j*)acridine
 carcinogenic properties in cigarette smoke from, 265

7H-Dibenzo(*c,g*)carbazole
 carcinogenic properties in cigarette smoke from, 265

Dibenzo(*a,i*)pyrene
see Benzo(*rs*)pentaphene

Diethylnitrosamine
 suspected carcinogenic properties in cigarette smoke from, 265

7,12-Dimethyl-benz(*a*)anthracene
see Benz(*a*)anthracene, 7,12-dimethyl-

Dimethylnitrosamine
 suspected carcinogenic properties in cigarette smoke from, 265

2,3-Diphosphoglycerate
 effects of carbon monoxide on, 60-61

DNA
see Deoxyribonucleic acid

Dogs
 atherogenic effects of nicotine in, 120
 bladder neoplasms in, fed 2-naphthylamine, 296
 bradycardia and tachycardia in, following nicotine injection, 57-58
 bronchogenic carcinoma induction in, from cigarette smoke inhalation, 269, 270
 cigarette smoke instillation or implantation effects on tracheobronchial tree of, 268, 347
 death in, causes from cigarette smoke inhalation, 271
 effect of cigarette smoke on pulmonary clearance in, 164, 170
 fetal bronchial tubes of, effect of cigarette smoke on, 345
 lungs of, cigarette smoke effects on surfactant activity, 172, 225
 lung neoplasms following cigarette smoke inhalation, 239, 277
 lung neoplasms in, types and lobes where found, 269, 272-273
 myocardium of, nicotine effects on, 58
 neoplasm development in smoking, percentages of, 274
 pulmonary histological changes in cigarette smoke inhaling, 158, 159-160
 respiratory tract of, cigarette smoke inhalation effects on, 268, 352, 353
 smoke induced bronchoconstriction in, atropine effects, 163
 smoking and nicotine effects on blood lipids in, 127-128
 smoking and nicotine effects on cardiovascular function in, 107-112
 smoking and nicotine effects on catecholamine levels in, 119

Donkeys
 effect of cigarette smoke on pulmonary clearance in, 164, 171

Ducks
 cigarette smoke instillation or implantation effects on tracheobronchial tree of, 346

Duodenal ulcer
see Peptic ulcer

Dusts
 COPD development from, 153, 218

Egypt
 relation of human pulmonary histology and smoking, 163

Electrocardiograph
 findings on, CHD mortality relationship to, 42
 reading abnormalities, relationship to smoking and CHD, 45, 47

Electrophoresis
 use in determining serum level of alpha₁-antitrypsin, 151

Emphysema
 alpha₁-antitrypsin absence type genetic factors, 150
 cigarette smoking effects on, 9
 development in dogs following cigarette smoke inhalation, 271
 development of, relation of cadmium in smoke to, 154
 grade II or III, smokers vs. nonsmokers, 162
 mechanism in alpha₁-antitrypsin absence type of, 151
 mortality from, effect of cigarette smoking on, 175
 mortality rates from, in 1967, 139
 pulmonary, definition, 139

Employment
see Occupations

England
see United Kingdom

Enzymes
see also Papain
 activity of, effect of smoking, 165
 aryl hydrocarbon hydroxylase activity in placentas at childbirth, 410
 aryl hydroxylase, effect of nickel in cigarette smoke on induction of, 257
 benzo(*a*)pyrene hydroxylase, activity in placentas of smoking mothers, 410
 carbonic anhydrase, carbon monoxide inhibition in fetal cord blood of smoking mothers, 407
 carbonic anhydrase, decrease in activity in fetal cord blood in smoking mothers, 409

Epidermoid carcinoma
see Carcinoma, epidermoid

- Epinephrine
levels in arteries, cigarette smoking effects on, 57
- Epitheliomas
lip, relationship of tobacco use with, 361
- Epoxides
suspected carcinogenic agents in cigarette smoke, 265
- Esophageal neoplasms
frequency in smokers vs. nonsmokers, 12, 238
induction in animals by nitrosamine, 292
methods and results of retrospective studies of tobacco use, 289, 375-378
mortality rates in U.S. for 1967, 289
relationship to smoking, 293
- Esophagus
basal cells of epithelium of, atypical nuclei in male smokers 292, 379-380
- Ethanol
see Alcohol
- Ex-smokers
see Smokers (former)
- Factory workers
see plant workers under Occupations
- Fatty acids
blood, effect of smoking on levels of, 65
levels in smokers vs. nonsmokers, 102
rise in blood serum after smoking, 36
suspected carcinogenic agents of cigarette smoke, 266
- Fetus
heart beats in, increase in smoking mothers, 408
tissues of, effects of elevated carboxyhemoglobin on, 407
- Fibrosis
in lung, smokers vs. nonsmokers, 161
- Fibrillation
ventricular, death from, 36
- Filters
see Cigarette filters
- Finland
blood pressure differences in smokers vs. nonsmokers in, 103
COPD morbidity in smokers of, 200
lung neoplasms in, retrospective smoking study of methods in, 325, 327
lung neoplasm mortality in, relationship to tobacco use, 245-246
peptic ulcer in, methods and results for retrospective and cross section studies of smoking and, 426, 428
serum lipid differences in smokers vs. nonsmokers of, 98, 99
smoking and nicotine effects on human blood lipids in, 124
- Fluoranthene
alcoholic solution of, penetrability of esophageal epithelium, 292
- Flax mill workers
see Occupations
- Former smokers
see Smokers (former)
- Formosa
acute effect of cigarette smoke on human pulmonary function in, 169
- France
bladder neoplasms in, methods and results in retrospective studies of smoking and, 381-383
CHD mortality and morbidity in, 94, 97
COPD mortality of smokers in, 201
cigarette smoke effects on animal lung tissue in, 343
cigarette smoke effects on chicken embryos in, 344
cigarette smoke inhalation effects on rat respiratory tract, 349
esophageal neoplasms in, retrospective studies of tobacco use with, 378
laryngeal neoplasms in, relationship to tobacco use, 355, 357
lung neoplasms in, retrospective smoking study of methods in, 326
relationship of tobacco use and neoplasms of oral cavity, 363
- Framingham Heart Study
morbidity ratios in CHD, 24
- Fungicides
concentration in cigarette smoke, 265, 266
- Gastric ulcer
see Peptic ulcer
- Genetics
factors of, cigarette smoking relationship, 5
factors of, in COPD pathogenesis, 148, 150-152, 205
twin-studies, effects of smoking, 49-52, 99
- Germany
CHD morbidity and mortality in, 95-96, 97
cigarette smoke inhalation effects on animal respiratory tract in, 350
laryngeal neoplasms in, relationship to tobacco use, 355
lung neoplasms in, retrospective smoking study of methods in, 323, 325, 326
polonium-210 levels in lungs of smokers in, 336
smoking and nicotine effects on human blood lipids, 125
- Glossary
of terms used in smoking and ventilatory function, 215
- Glucose
metabolism and insulin response, alteration effects on myocardial response, 66
- Glycogen
levels in mice lung exposed to cigarette smoke, 161
- Government employees
see Occupations
- Graphite
respiratory tract carcinoma in workers exposed to, 256
- Great Britain
see United Kingdom
- Guanethidine
blockage of nicotine cardiac stimulation by, 57
- Guinea pigs
lung neoplasm development following chronic nickel carbonyl or dust inhalation, 256

- lungs of, cigarette smoke effects on surfactant activity, 225
- respiratory changes in, exposed to cigarette smoke, 162
- Hamsters**
 - benzo(a)pyrene inhalation by, effect of asbestos dust on carcinoma induction, 257
 - bladder neoplasms in, fed 2-naphthylamine, 296
 - cigarette smoke instillation or implantation effects on tracheobronchial tree of, 268, 346-348
 - laryngeal malignancies in, following smoke inhalation, 12
 - laryngeal neoplasms following cigarette smoke inhalation, 239
 - larynx of, effect of cigarette smoke inhalation on, 281, 284
 - lung and embryos, effects of cigarette smoke tars on, 343-344
 - pulmonary changes from chronic nitrogen dioxide inhalation, 220
 - respiratory tract of, C-14 labeled particulates deposition in, 281-282
 - respiratory tract of, cigarette smoke inhalation effects on, 268, 351
- Health Insurance Plan (NYC)**
 - myocardial infarction in pipe and cigar smokers under, 32, 38-39
- Heart**
 - see also* Arrhythmia, bradycardia, myocardium and tachycardia
 - cardiac rhythm of, effect of nicotine on, 36
 - fetal, increased rate by maternal smoking, 408
 - myocardium of, nicotine effects on oxygen demand, 38
 - myocardium of, cigarette smoking effect on, 5, 8
 - rate, relationship to smoking and CHD, 45, 47
- Heart disease**
 - see* Cardiovascular diseases and coronary disease
- Heights**
 - decreased, in children of smoking mothers, 407
- Hematite dust**
 - respiratory tract neoplasms in hamsters exposed to, 348
- Hematocrit**
 - infant, smoking mother effects on, 407, 409
 - variations in, effect on coronary blood flow, 66
- Hemoglobin**
 - see also* Carboxyhemoglobin
 - affinity for oxygen, CO effects on 2,3-diphosphoglycerate control of, 60-61
 - variations in, effect on coronary blood flow, 66
- Hens**
 - see* Chickens
- Heterocyclic compounds**
 - carcinogenic properties in cigarette smoke, 264, 265
- Hexamethonium**
 - blockage of nicotine cardiac stimulation by, 57
- HIP of NYC**
 - see* Health Insurance Plan (NYC)
- Hookahs**
 - smokers of, laryngeal neoplasm induction in, 355
- Hungary**
 - retrospective smoking study of methods for lung neoplasms in, 328
- Hydrocarbons**
 - see* Aromatic compounds heterocyclic compounds
- Hydrogen cyanide**
 - in cigarette smoke, effects on body oxidative metabolism, 62
- 3-Hydroxyanthranilic acid**
 - see* Anthranilic acid, 3-hydroxy-
- 3-Hydroxykynurenine**
 - excretion of, smoking effects on, 296
- Hydroxyproline**
 - level in mice lung exposed to cigarette smoke, 161
- Hypertension**
 - see* Blood pressure
- Hypoxemia**
 - arterial, carbon dioxide effects on, 61, 75
- Hypoxia**
 - aortic atheromatosis development in rabbits exposed to, 64
 - postoperative, development in smokers, 174, 230
 - postural, mechanism in asymptomatic smokers vs. nonsmokers, 147
- Iceland**
 - lung neoplasms in, relationship to tobacco smoking, 244
- Indeno(1,2,3-cd)pyrene**
 - carcinogenic properties in cigarette smoke from, 265
- India**
 - esophageal neoplasms in, retrospective studies of tobacco use with, 378
 - laryngeal neoplasms in, relationship to tobacco use, 355, 356
 - relationship of smoking to tuberculosis in, 227
 - relationship of tobacco use and neoplasms of oral cavity in, 362, 366
 - smoking and nicotine effects on human cardiovascular system, 117
 - smoking relationship to thrombosis in, 131
- Indole, 1-methyl-**
 - possible initiator in tobacco carcinogenesis, 265
- Industrial workers**
 - see* plant workers under Occupations
- Industrial hazards**
 - effect of dust on COPD development, 175
 - effects on COPD development in smokers, 153-154, 218-219
- Infant**
 - see also* Neonate
 - sudden death in, relation of smoking and nonsmoking mothers, 407
- Influenza virus**
 - effect on dogs inhaling cigarette smoke, 351

- resistance of mice following cigarette smoke inhalation, 173
- Inhalation studies
 - see *under* Cigarette smoke
- Ireland
 - acute effect of cigarette smoke on human pulmonary function, 168
 - CHD mortality and morbidity in smokers and nonsmokers in, 94
 - CHD mortality and morbidity in, 96
 - lung neoplasms in, retrospective smoking study of methods in, 328
 - maternal smoking and infant weight, 399
 - methods used in smoking study and human pregnancy, 394, 396
 - northern, mortality rates from COPD, 144
 - occupational exposure and smoking relationships to COPD in, 218
 - relationship of lung neoplasms to smoking, air pollution and residence in, 254
 - serum lipid differences in smokers vs. nonsmokers in, 99
 - smoking and nicotine effects on human peripheral vascular system, 133
 - smoking relationship to thrombosis in, 130
- Israel
 - cigarette smoke effects on animal embryos in, 343
 - mortality rates from COPD in, increase, 140
- Italy
 - human experimental data on smoking and pregnancy, 409
 - serum lipid differences in smokers vs. nonsmokers in, 100
 - tracheobronchial tree changes in smokers and nonsmokers in, 263
- Japan
 - bladder neoplasms in, methods and results in retrospective studies of smoking and, 382, 384
 - CHD mortality and morbidity in, 96
 - cigarette smoke effects on human fetal lung tissue in, 343
 - esophageal neoplasms in retrospective studies of tobacco use in, 378
 - kidney and bladder neoplasms of smokers in, 295
 - lung neoplasms in, retrospective smoking study of methods in, 326, 328
 - lung neoplasm mortality of smokers and nonsmokers in, 243
 - mortality ratios from esophageal neoplasms in, 291
 - mortality ratios from pancreatic neoplasms in cigarette smokers in, 298
 - relationships of lung neoplasms to smoking, air pollution, and residence in, 255
- Kidney neoplasms
 - mortality rates in U.S. for 1967, 296
 - relationship of tobacco use, 13, 299
 - in smokers and nonsmokers, 238, 294-295
- Korea
 - relation of human pulmonary histology and smoking in, 255
- tracheobronchial tree changes in smokers and nonsmokers of, 259
- Lactones
 - suspected carcinogenic agents in cigarette smoke, 265
- Laparotomy
 - postoperative pulmonary complications following, in smokers vs. nonsmokers, 174
- Laryngeal neoplasms
 - development in hamsters following cigarette smoke inhalation, 239
 - development in smokers, 12, 281
 - mortality in smokers vs. nonsmokers, 237-238
 - mortality ratios from, 277-279
 - relationship to tobacco use and development of, 354-357
 - relative risk ratios from tobacco use, 277, 358
 - U.S. mortality in 1967, 277
- Larynx
 - epithelial changes in, classification of, 281, 283
 - hamster, C-14 labeled particulate deposition in, 281-282
- Laws
 - PL 89-92, requirements for smoking hazards literature review, 7
 - PL 91-222, requirements for smoking hazards review, 7
- Lip neoplasms
 - relationship of tobacco use, 361, 362, 365, 367
 - relationship to pipe smoking, 289
- Lipids
 - blood effect of smoking on levels of, 65-66, 123-128
 - serum, differences in smokers vs. nonsmokers, 41, 98-102
- Lipoproteins
 - infiltration in arterial walls, carbon monoxide effects on, 63
 - in smokers vs. nonsmokers, 99-102
- Liver
 - cirrhosis of, rates among cigarette smokers, 5
- Longshoremen
 - see Occupations
- Luminescence
 - techniques of, use in determining aromatic hydrocarbon in urine, 297
- Lung diseases
 - see Bronchopulmonary diseases, adenocarcinoma, carcinoma, tuberculosis
- Lungs
 - fibroses in, smokers vs. nonsmokers, 161
 - hamster, C-14 labeled particulates deposition in, 281-282
 - human, effects of cigarette smoke on tissue from, 343-345
- Lung neoplasms,
 - air pollution role in etiology of, 11
 - cause and effect relationship of smoking, 276
 - cigarette smoking risks, 11
 - development in dogs following cigarette smoke inhalation, 239
 - effect of sex on development, 11

- environmental and atmospheric factors of, 252-255
 - groupings, 246-334
 - group characteristics of tobacco use in smokers and nonsmokers, 240, 244, 329-333
 - histology and smoking relationships, 246-249
 - mortality expected in U.S. in 1970, 237, 239
 - mortality from chromium compounds, 257-258
 - mortality in cigarette smokers by duration, 240, 244
 - mortality in smelter workers exposed to arsenic, 257
 - mortality in smokers and nonsmokers, 240-243
 - mortality, in smokers in Norway and Finland, 245-246
 - occupational exposure effects on pathogenesis of, 12
 - prevalence in males and females by tumor type, 246, 250
 - reduction in number using filter-type cigarettes, 275
 - relationship of asbestos and smoking to, 257
 - relationship of female smoking, 246, 251
 - relationship of smoking to, 237
 - retrospective study methods for smoking relationships, 240, 323-328
 - smoking cause and effect relationship, 3
 - smoking habit study of patients with, 3
 - types implicated in smoking, 237
 - U.S. mortality rates for 1939 vs. 1967, 239
- Macrophages**
effect of cigarette smoke of action on staphylococcus, 165
- Mammals**
see also specific mammals
cells of, effect of cigarette smoke tars on, 343
- Medical students**
see Occupations
- Methylbenzo(a)pyrene**
see Benzo(a)pyrene, 1-methyl-
- 9-Methyl carbazole**
see Carbazole, 9-methyl-
- Methylchrysenes**
see Chrysene, 1-methyl-
- Methyl-indole**
see Indole, 1-methyl-
- Methyl-n-butyl nitrosamine**
see Butylamine, n-methyl-nitroso-
- N-Methylnicotinamide**
see Pyridinium compounds, 3-carbamoyl-1-methyl-
- Mice**
bladder neoplasms in, induction by tryptophan metabolites, 296
- embryo, lethal effects of nicotine on, 411
- esophageal epithelium of, alcoholic benzo(a)pyrene penetrability of, 292
- esophageal epithelium of, oil desolved benzo(a)pyrene penetrability of, 292
- lungs of, effects of cigarette smoke on, 343, 344
- lung neoplasm incidence in, from chromium oxide dust exposure, 258
- pulmonary carcinoma induction in, following asbestos dust inhalation, 257
- pulmonary changes from chronic nitrogen oxide inhalation, 161, 220
- pulmonary changes in cigarette smoke inhaling, 159
- pulmonary clearance in, cigarette smoke effects on, 170
- resistance to pneumonia bacteria following cigarette inhalation, 173
- respiratory tract of, cigarette smoke inhalation effect on, 268-269, 349-353
- skin painting of, smoke condensates effects on, 267, 337-342
- Miscarriages**
see Abortion, spontaneous
- Mollusks**
ciliary function in, effect of cigarette smoke on, 223
- Monkeys**
atherogenic effects of carbon monoxide and hypoxia, 64
- ciliary function in, effect of cigarette smoke on, 222
- fetal bronchial tubes of, effects of cigarette smoke on, 345
- Rhesus, development of bladder neoplasms from 2-naphthylamine, 296
- squirrel, nitrogen oxide effects on resistance to pneumococcus, 173
- Morbidity ratio**
CHD in smokers with predisposing factors, 24
- CHD in smokers vs. nonsmokers, 21-22, 24, 30-35
- CHD, relation to smoking, 32-35, 37, 39
- CHD, retrospective studies, 40, 93-97
- in Danish twins, smoking effects on, 49-51
- development of COPD in smokers vs. nonsmokers, 145, 195-205
- Mortality rates**
from bladder neoplasms in U.S. for 1967, 293
- from bronchopulmonary disease, 141-145
- cerebrovascular disease, smokers vs. nonsmokers, 66-67, 68-70
- CHD, paired combinations of high risk characteristics in, 25
- CHD, retrospective studies, 40, 93-97
- CHD in smokers vs. nonsmokers, 24, 26-29
- CHD in U.S., 21
- in Danish twins, smoking effects on, 51
- from esophageal neoplasms in U.S. in 1967, 289
- from kidney neoplasms in U.S. for 1967, 296
- from lung neoplasms for 1939 vs. 1967 in U.S., 239
- from lung neoplasms expected in 1970, 237, 239
- from lung neoplasms in smelter workers exposed to arsenic, 257
- from oral neoplasms in 1967, 285

- from peptic ulcer in U.S. in 1967, 423
- in former smokers, relation to CHD, 46, 47-48
- in Swedish twins, smokers vs. nonsmokers, 51
- smokers vs. nonsmokers, 3
- U.S. male veterans from CHD, 26, 38
- Mortality ratios**
 - CHD with high risk characteristics, estimated, 25
 - from esophageal neoplasms, prospective and retrospective studies, 289-291
 - from laryngeal neoplasm, 277-279
 - from lung neoplasms in smokers in Norway and Finland, 246
 - from lung neoplasms, in males by cigarette smoking duration, 240, 244
 - from pancreatic neoplasms in smokers and nonsmokers, 298-299
 - from peptic ulcer in smokers and nonsmokers, 424
 - smokers vs. nonsmokers, from lung neoplasms, 240-243
- Mouth neoplasms**
 - frequency in smokers and nonsmokers, 238
 - smoking induced, 12
- Mucopolysaccharides**
 - function as surfactants in lung tissue, 172
- Mussels**
 - ciliary function in, effects of cigarette smoke on, 221, 222
- Myocardium**
 - effects of hydrogen cyanide in smoke on, 62
 - oxygen consumption in nicotine stimulated, 59
 - oxygen requirements for, nicotine effects, 58
- 2-Naphthylamine**
 - development of bladder carcinomas and papillomas in dogs, hamsters and monkeys given, 296
 - suspected bladder carcinogen in tobacco smoke, 265
- National Center for Health Statistics**
 - survey of U.S. smoking habits by, 5-6
 - survey on relationship of smoking and incidence of respiratory disease, 173
- National Clearinghouse for Smoking and Health**
 - responsibilities, 7
 - 1970 survey of smoking, 6
- National Cooperative Pooling Project**
 - mortality statistics from coronary disease, 21-22
- National Library of Medicine**
 - assistance in literature review on smoking, 7
- Natural gas**
 - respiratory tract carcinoma in workers exposed to, 256
- Negroes**
 - see Blacks*
- Neonate**
 - see also Fetus, pregnancy, prematurity*
 - birth weight, effect of maternal smoking on, 389, 397-399
- death, comparison of stillbirth and abortions in smoking and nonsmoking mothers, 395, 405-406
- death, differences of birth weight and, in smoking and nonsmoking mothers, 404
- death, smoking mothers effects on 415 rats, LD₅₀ nicotine determination, 412
- Neoplasms**
 - see also specific neoplasms, adenocarcinoma, carcinoma, lung neoplasms, etc.*
 - adenomatous, induction in mice by cigarette smoke inhalation, 350
 - bladder, in smokers and nonsmokers, 293-295, 381-384
 - bladder, methods of retrospective studies of smoking and, 293, 381-384
 - bladder, relationship of tobacco usage to, 299
 - bladder, relationship to cigarette smoking, 13, 299
 - bladder, U.S. mortality in 1967, 293
 - development in smoking dogs, percentages of, 274
 - esophageal, frequency in smokers and nonsmokers, 12, 238
 - esophageal, methods and results of retrospective studies of tobacco use in, 289, 375-378
 - esophageal, mortality ratios, 289-291
 - esophageal, mortality rates for U.S. in 1967, 289
 - esophageal, relationship to smoking, 293
 - kidney, mortality rates in U.S. for 1967, 296
 - kidney, relationship to tobacco use, 13, 299
 - kidney, in smokers and nonsmokers, 238, 294-295
 - laryngeal, 12, 237-239, 281
 - laryngeal, relationship of tobacco use and development of, 354-357
 - laryngeal, relative risk ratios from tobacco use, 277, 358
 - laryngeal, U.S. mortality in 1967, 277
 - lip, relationship to smoking, 289
 - lip, relationship to tobacco use, 361, 362, 365, 367
 - mammalian, cigarette smoke effect on, 343
 - oral cavity, relationship of tobacco use, 285, 361-367
 - oral cavity, relationship to smoking, 289
 - pancreas, relationship to smoking, 298-299
- Netherlands**
 - cigarette smoke inhalation effects on mice respiratory tract in, 349
 - lung neoplasms in, retrospective smoking study of methods for, 323
 - serum lipid difference, in smokers vs. nonsmokers of, 101
- New York City**
 - myocardial infarctions in cigar and pipe smokers in, 32, 38-39
- New Zealand**
 - human experimental data on smoking and pregnancy, 408-409
- Nickel compounds**
 - suspected carcinogenic agents in cigarette smoke, 265

Nickel workers
see Occupations

Nicotine
 atherogenic effects of 120-122
 effect on blood lipids, 123-128
 effect on blood pressure, 36
 effects on cardiac rhythm of heart, 36
 effects on cardiovascular system, 56-58, 107-118
 effects on catecholamine release from adrenals, 36, 119
 effects on heart rate, 36
 effects on myocardium oxygen demand, 38
 effects on myometrial strips in gravidic women, 408
 effects on peripheral vascular system, 72, 75, 133-134
 effects on pregnancy, 411-414
 induction of necrosis in arterial walls, 63
 neurogenic effects of, 57

Nitrogen dioxide
 pulmonary changes in rodents chronically inhaling, 161, 220

Nitrogen oxide
 effects on resistance of squirrel monkeys to pneumococcus, 173

4-Nitroquinoline 1-oxide
 alcoholic solution of, development of papillomas in mice drinking, 292

N-Nitrosamines
 carcinogenicity in cigarettes smoke, 264-266
 esophageal neoplasms induced in animals by, 292

Nitrosopiperidine
see Piperidine, nitroso-

Nitrosopyrrolidine
see Pyrrolidine, nitroso-

N¹-methylnicotinamide
 urinary excretion of, smoking effects on, 297

Nonsmokers
see also Smokers vs. nonsmokers
 carboxyhemoglobin effects on oxygen uptake, 61

Norway
 lung neoplasms in, for pipe smokers, 244
 lung neoplasm mortality in, relationship to tobacco use, 245-246
 tracheobronchial tree changes in smokers and nonsmokers of, 259

Oat cell carcinoma
see Carcinoma, oat cell

Obesity
 relationship to CHD mortality, 43
 relationship to smoking and CHD, 43-45
 relationship with smoking in peripheral arteriosclerosis, 72

Occupations
see also Industrial hazards
 asbestos workers, respiratory tract carcinoma, 256
 asbestos workers, lung neoplasm mortality in smoking, 257
 bank employees, smoking and COPD, 198
 coal miners, impaired pulmonary function in smoking, 163
 coal miners, respiratory tract carcinoma, 256
 coal miners, smoking and COPD, 153, 197, 218-219
 coal miners, smoking and ventilatory function, 207
 flax mill workers, smoking and COPD, 199
 government employees, blood pressure differences in smokers vs. nonsmokers, 99
 longshoremen, mortality from smoking-related cerebrovascular disease, 70
 longshoremen, mortality rates from CHD in, 28
 longshoremen, smoking and COPD, 200
 longshoremen, smoking and ventilatory function, 208
 medical students, serum lipid differences in smokers vs. nonsmokers, 98
 medical students, smoking and nicotine effects on blood lipid levels, 124
 medical students, smoking and thrombosis relationships, 130
 medical students, smoking and ventilatory function, 209-210
 nickel workers, lung neoplasms in, 256
 physicians, bladder and kidney neoplasms in smoking, 293, 294
 physicians, cessation of smoking effect on COPD, 142
 physicians, COPD mortality rates, 149
 physicians, decline in cigarette smoking rates, 48
 physicians, mortality from smoking-related cerebrovascular disease, 68
 physicians, mortality rates from CHD, 26
 physicians, mortality ratios from esophageal neoplasms, 290
 physicians, mortality ratios from peptic ulcer in smoking and nonsmoking, 424
 physicians, pulmonary function following cessation of smoking, 149
 physicians, smoking and ventilatory function, 209-210, 213
 plant workers, occupational exposure and smoking relationships to COPD, 153, 218, 219
 plant workers, smoking and COPD, 198
 plant workers, smoking and ventilatory function, 206-208
 post office workers, blood pressure differences in smokers vs. nonsmokers, 104
 post office workers, smokers and ventilatory function, 209
 post office workers, smoking and COPD, 200, 202
 prisoners, serum lipid differences in smokers vs. nonsmokers, 100
 prisoners, smoking and nicotine effects on peripheral vascular system, 133
 railroad employees, coronary heart disease, morbidity in smoking, 34
 railroad employees, mortality and morbidity from CHD, 97
 railroad employees, mortality rates from CHD, 28
 smelter workers, lung neoplasm mortal-

- ity from arsenic exposure, 257
- soldiers, smoking and COPD, 197
- steel workers, COPD development from dust exposure, 153
- students, carbon monoxide effects on blood lipids, 129
- students, infectious respiratory disease in smokers vs. nonsmokers, 228-229
- students, mortality from smoking-related cerebrovascular disease, 68
- students, mortality rates from CHD, 28
- students, smoking and COPD, 201
- students, smoking and nicotine effects on blood lipid level, 125
- students, smoking and thrombosis relationships, 130
- students, smoking and ventilatory function, 211
- telephone company employees smoking and COPD, 200
- textile workers, occupational exposure and smoking relationship to COPD, 218-219
- transportation employees, smoking and COPD, 198, 202
- transportation workers, air pollution relationship to COPD, 216
- transportation workers, smoking and ventilatory function, 207, 212
- utility company employees, CHD morbidity in smoking, 30
- uranium miners, lung neoplasms in smokers and nonsmokers, 256
- veterans, bladder and kidney neoplasms in smoking, 294-295
- veterans, COPD mortality rates, 143
- veterans, CHD morbidity in smoking, 32
- veterans, effects of smoking on twin, 50
- veterans, lung neoplasm mortality in smoker and nonsmoker, 241-243
- veterans, mortality rates from CHD, 26, 38
- veterans, mortality from smoking-related cerebrovascular disease, 69
- veterans, mortality ratios from esophageal neoplasms, 290
- veterans, mortality ratios from peptic ulcer in smokers vs. nonsmokers, 424
- Oleic acid
 - suspected carcinogenic agent in cigarette smoke, 266
- Olive oil
 - penetrability of benzo(a)pyrene in mice esophageal epithelium, 292
- Oral cavity neoplasms
 - estimated incidence in U.S. for 1970, 284
 - mortality from in 1967, 285
 - relationship of tobacco use, 285, 289, 361-367
- Organs
 - cultures of, cigarette smoke effects on cell growth and reproduction, 267, 343-345
- Oropharynx neoplasms
 - frequency in smokers and nonsmokers, 238
- Oxygen
 - see also Hypoxemia
 - myocardial consumption of, following nicotine stimulation, 58, 75
- transport in body, carbon monoxide effects, 60, 75
- uptake in nonsmokers with specific carboxyhemoglobin levels, 61, 75
- Palate
 - hamster, C-14 labeled smoke particulates deposition in, 281-282
- Pancreatic neoplasms
 - relationship to smoking, 13, 238
 - relationship of smoking to mortality from, 298-299
- Papain
 - pulmonary effects on rats exposed to cigarette smoke with, 163
- Papillomas
 - development in mice drinking alcoholic benzopyrene, 292
 - formation following skin painting with smoke tars, 337-339, 341
 - induction in hamsters exposed to benzo(a)pyrene, 346-347
- Pentolinium
 - blockage of nicotine cardiac stimulation by, 57
- Peoples Gas Light and Coke Co.
 - study of CHD, serum cholesterol and smoking relationships, 43
- Peptic ulcer
 - antacid efficacy and healing of, effects of cigarette smoking on, 423
 - development in smokers, 13
 - mortality from, in U.S. in 1967, 423
 - mortality ratios from, in smokers and nonsmokers, 424
 - retrospective and cross section study methods for smoking relationship to, 425-427
- Peroxides
 - suspected carcinogenic agent in cigarette smoke, 265
- Personality characteristics
 - relationship to CHD and smoking, 48-49, 105-106
- Pesticides
 - content in cigarette smoke, 265, 266
- Phagocytosis
 - pulmonary alveolar, in smokers vs. nonsmokers, 165
- Pharyngeal neoplasms
 - frequency in smokers vs. nonsmokers, 238
 - relationship to tobacco use, 362-364, 366
- Phenol
 - suspected carcinogenic agent of cigarette smoke, 266
- Phospholipids
 - function as surfactants in lung tissue, 172
 - smokers vs. nonsmokers, 99-100, 102
- Physical activity
 - relationship to CHD and smoking, 41, 43, 44
 - relationship to myocardial infarction, smokers vs. nonsmokers, 44
- Physicians
 - see Occupations
- Piperidine, nitroso-

- suspected carcinogenic properties in cigarette smoke from, 265
- Pipe smokers**
 atypical nuclei in male esophageal epithelium, 379
 bladder neoplasms in, 293-294
 cell rows and atypical cells in vocal cords of, 280, 359-360
 COPD morbidity in, 146, 197-198, 201-205
 development of chronic bronchopulmonary disease, 10
 development of esophageal neoplasms, 13, 293
 development of lung cancer, 11
 development of oral neoplasms, 12
 esophageal neoplasm mortality ratios, 290
 kidney neoplasms in, 294-295
 lack of risk in CVD, 67
 laryngeal neoplasms induction, 12, 354-357
 lung neoplasm incidence in Norway, 244
 lung neoplasm incidence in rural Switzerland, 244
 lung neoplasm mortality in, 324-327
 mortality rates from COPD, 142-143, 145
 mortality ratios from pancreatic neoplasms, 298
 mortality ratios from peptic ulcer, 424
 myocardial infarction in, 32, 38-39
 peptic ulcer in, 427
 relationship to infectious respiratory disease, 227
 relationship to laryngeal neoplasm development, 281
 relationship to lip neoplasms, 289
 relationship to oral cavity neoplasms, 361-364, 367
 risk of CHD, 8
 risks on lung neoplasm development, 276
- Placenta**
 ability to hydroxylate benzo(a)pyrene in smoking mothers, 407
- Platelets**
 adhesiveness of increased, from cigarette smoking, 9
 aggregation of, cigarette smoking effects on, 36
 blood, effect of smoking, 66, 75
- Poland**
 bladder neoplasms in, methods and results in retrospective studies of smoking and, 382, 383
 CHD mortality and morbidity in, 96
 esophageal neoplasms in, retrospective studies of tobacco use with, 378
 laryngeal neoplasms in, relationship to tobacco use, 357
 relationship of tobacco use and neoplasms of oral cavity in, 364
 serum lipid differences in smokers vs. nonsmokers in, 100, 102
 smoking and nicotine effects on human blood levels in, 124
 smoking relationships to thrombosis in, 131
- Pollution**
 see Air pollution
- Polonium-210**
 suspected carcinogenic agent in cigarette smoke, 265-267, 335-336
- Post office workers**
 see Occupations
- Postoperative pulmonary complications**
 see Respiratory system
- Potassium-40**
 present in tobacco leaf, 266
- Pregnancy**
 see also Abortion (spontaneous), placenta, stillbirth, neonate
 human, methods used in smoking study of, 391-396
 maternal smoking during, effect on fetal growth and weight, 389, 397-399
 maternal smoking during, effects on fetal growth, 13, 415
 nicotine effects on myometrial strips in, 408
 unsuccessful, smoking effects on, 13
- Prematurity**
 maternal smoking and, 390, 400-403
- Prisoners**
 see Occupations
- Proteins**
 see Lipoproteins
- Protozoae**
 ciliary function in, effect of cigarette smoke on, 165, 224
- Public Health Service**
 review of medical literature on smoking hazards, 7
 1967 study of, starting point for new studies, 4
- Public laws**
 see Laws
- Puerto Rico**
 esophageal neoplasms in, retrospective studies of tobacco use with, 378
 relationship of tobacco use and neoplasms of oral cavity in, 367
- Pulmonary system**
 see Respiratory system
- Pyrrolidine, nitroso-**
 suspected carcinogenic properties in cigarette smoke from, 265
- Rabbits**
 atherogenic effects of carbon monoxide and hypoxia, 64
 atherogenic effects of nicotine, 120-122
 blood lipids in, smoking and nicotine effects on 127
 cardiovascular function in, smoking and nicotine effects, 108, 109
 ciliary function in, cigarette smoke effect on, 221-222
 cholesterol fed, carbon monoxide effects on, 65-66
 offspring of, nicotine and smoke effects on birth weight, 407
 offspring, smoking effects on stillbirth and mortality, 411
 pregnant, tritium-labeled nicotine effects in, 413
 pulmonary changes in cigarette smoking, 159
 pulmonary clearance in, cigarette smoke effect on, 164, 170, 171

- skin painting, smoke condensate effects on, 267, 338
- Railroad employees
 - see* Occupations
- Rats
 - atherogenic effects of nicotine in, 120, 121
 - blood lipids in, nicotine and smoke effects, 128
 - ciliary function in, cigarette smoke on, 221, 222
 - LD₅₀ nicotine determination in female, 412
 - lung neoplasms, from intrabronchial implanting of chromium compounds, 258
 - lung neoplasms, from nickel carbonyl and dust inhalation, 256
 - lungs, cigarette smoke effects on surfactant activity, 172, 225
 - offspring, nicotine and smoke effects on birth weight, 407
 - pregnant, aromatic compound stimulation of placental BP-hydroxylase activity, 414
 - pregnant, fetal wastage and neonate death in nicotine and smoking, 411
 - pulmonary carcinoma induction following asbestos dust inhalation, 257
 - pulmonary changes from chronic nitrogen dioxide inhalation, 161, 220
 - respiratory tract of, cigarette smoke inhalation effects, 268, 349, 353
 - skin painting, smoke condensates effects, 267, 340
 - trachea of, cigarette smoke effects, 343
 - tracheal ligation of, cigarette smoke and papain effects on, 163
 - tracheobronchial tree of, cigarette smoke effects on, 268, 346-349
- Reading ability
 - in children of smoking mothers, 407
- Reserpine
 - nicotine cardiac stimulation blockage by, 57
- Respiratory system
 - see also* Bronchopulmonary disease, larynx, lungs, trachea
 - acute effect of cigarette smoke on human pulmonary function, 163, 166-169
 - animal, cigarette smoke instillation or implantation effects on, 268, 346-348
 - animal, effect of cigarette smoke inhalation on, 268-269, 349-353
 - effect of cigarette and cigar smoke on bronchial reactivity, 164
 - effect of cigarette smoke on human ciliary function, 165, 221-224
 - effect of cigarette smoke on human pulmonary clearance, 164, 170
 - glossary of terms used in testing, 215
 - histological changes in smokers, 154-157
 - improvements in function following smoking cessation, 148, 149
 - pathological changes in cigarette smokers, 175
 - postoperative complication in, of smokers vs. nonsmokers, 174-176, 230
 - pulmonary alveolar phagocytosis in smokers vs. nonsmokers, 165
 - pulmonary infarction in dogs inhaling cigarette smoke, 271
 - surface tension of, effect of cigarette smoke on, 172, 225
 - surfactant activity of, in smokers vs. nonsmokers, 172, 225
 - surfactants in, definition, 172
 - tests of function of, in smokers, 146-147, 206-214
- Respiratory tract diseases
 - see also* Asthma, bronchitis, bronchopulmonary disease, emphysema, pneumonia, tuberculosis
 - infectious, smoking effects on, 172, 226-229
 - infections, prevalency among smokers, 10, 176
 - pathological and cytological changes in, of smokers vs. nonsmokers, 258-263
 - ventilatory function in, smokers vs. nonsmokers, 175
- Rhodesia
 - retrospective smoking study of methods for lung neoplasms in, 328
- Rubidium-84
 - tracing capillary flow in coronary blood flow, 59
- Rural populations,
 - lung neoplasms in, suspected etiology of increased, 276
- Rural residences
 - lung neoplasm incidence in, in Switzerland, 244
 - relationships of lung neoplasm to smoking, air pollution, and, 252-255
- Russia
 - atherogenic effects of nicotine on rabbits in, 120
 - atherosclerosis autopsy studies in, 54
 - cigarette tar effects on rat tracheobronchial tree in, 348
- Saccharides
 - see* Mucopolysaccharides
- Saliva
 - interference in action of carcinogens on oral cavity, 288
- Sarcoma
 - formation following animal skin painting with smoke condensates, 338, 340
 - induction in rats by cigarette smoke injection, 346-347
- Scotland
 - see* United Kingdom
- Sex
 - ages of cigarette smokers by, 6
 - effect of, in alpha-antitrypsin deficiency emphysema, 151
 - effect of, on laryngeal neoplasm incidence development, 277
 - effect of, in mortality in cigarette smokers, 276
 - effect of, in lung neoplasms and tobacco use, 244, 329-333
 - lung cancer mortality by, 252
 - lung neoplasm development by, 11
 - mortality rates of cigarette smokers by, 3
 - ratios of, in lung neoplasm mortality in Norway and Finland, 245-246

Sheep
 pregnant, nicotine injection and smoke inhalation effects on, 414
Smelter workers
see Occupations
Smokers (former)
see also Cessation of smoking
 atypical nuclei in male esophageal epithelium in, 379-380
 CHD mortality probability in, 46
 incidence of CHD and mortality in, 46-48
 lung neoplasm mortality ratios in, 241-242
 lung neoplasms in, lowered rates, 11
 mortality rates from COPD, 175
 mortality rates from lung neoplasms, 276
Smokers vs. nonsmokers
see also Nonsmokers
 bladder neoplasms in, 293-295, 381-384
 cell rows and atypical cells in vocal cord of, 280, 359-360
 CHD mortality in, 21-22
 comparison of abortions, stillbirth and neonatal death in, 390, 405-406
 development of COPD in, 141, 145, 195-205
 differences in emphysema types in, 154, 156
 effect of cigarette smoke on post-operative pulmonary complications, 175
 effect of sex on mortality from CHD, 28-31
 esophageal epithelial cells with atypical nuclei in, 292
 esophageal neoplasm mortality ratios in, 290-291
 excretion of tryptophan metabolites in, 297
 frequency of esophageal neoplasms in, 238
 frequency of kidney neoplasms in, 238
 frequency of mouth and pharyngeal neoplasms in, 238
 frequency of urinary bladder neoplasms in, 238
 group characteristics in lung neoplasms and smoking in, 240, 244, 329-333
 laryngeal neoplasms in, relationship to tobacco use, 354-357
 lung fibrosis development in, 161
 lung neoplasm mortality ratios in, 240-243
 lung neoplasm mortality in uranium miners, 256
 morbidity ratios from CHD, 24
 mortality from cerebrovascular disease, 67-70
 mortality from CHD, 24, 26-29
 mortality from CHD in Swedish twins, 51
 mortality from laryngeal neoplasms in, 237-238
 mortality rates, 3
 mortality ratios of COPD in, 142-144
 mortality ratio from laryngeal neoplasms, 278-279
 mortality ratios from pancreatic neoplasms in, 298
 myocardial infarction relationships to physical activity, 44
 pathological and cytological changes in respiratory tract of, 258-263
 peptic ulcer in, correlated amounts of tobacco use, 427-428
 postoperative hypoxemia in, 174, 230
 postural hypoxemia mechanism in asymptomatic, 147
 postoperative pulmonary complications in, 174-175, 230
 pulmonary alveolar phagocytosis in, 165
 relation between CHD and serum cholesterol level, 43
 relationship to infectious respiratory disease, 172, 226-229
 serum lipids in, 41, 98-102
 surfactant activity in lungs of, 172, 225
 type of lung neoplasms in male and female, 250
Snuff
 dippers of, relationship to neoplasms of oral cavity, 287, 361, 364-365
Social adjustments
 in children of smoking mothers, 407
Socioeconomic relationships
 in COPD, 152-153, 216-217
Soldiers
see Occupations
South Africa
 esophageal neoplasms in, retrospective studies of tobacco use, 378
 occupational exposure and smoking relationship to COPD in, 219
 retrospective study of methods for lung neoplasms in, 328
 serum lipid differences in smokers vs. nonsmokers in, 99
Spontaneous abortions
see Abortions, spontaneous
Squamous cell carcinoma
see Carcinoma, epidermoid
Steel workers
see Occupations
Stearic acid
 suspected carcinogenic agent of cigarette smoke, 266
Stillbirths
 abortions and neonatal death and, in smoking and nonsmoking mothers, 390, 405-406
 effects of maternal smoking, 415
Students
see Occupations
Sugars
see Glucose, mucopolysaccharides
Surface tension
see Respiratory system
Surfactants
see Respiratory system
Sweden
 acute effects of cigarette smoke on human pulmonary function, 168
 blood pressure differences in smokers vs. nonsmokers in, 104
 CHD mortality and morbidity in, 97
 COPD morbidity in smokers in, 203, 205
 effect of cigarette smoke on animals ciliary function in, 221-224
 esophageal neoplasms in, retrospective

- studies of tobacco use with, 378
- genetic studies of twins in, smoking effects on, 50, 99
- laryngeal neoplasms in, relationship to tobacco use, 356
- relationship of tobacco use and lip neoplasms in, 361
- relationship of tobacco use and neoplasms of oral cavity, 364
- serum lipid differences in smokers vs. nonsmokers of, 99
- smoking and nicotine effects on human cardiovascular system, 115
- smoking and nicotine effects on human peripheral vascular system, 133
- tracheobronchial tree changes in smokers and nonsmokers in, 263
- Switzerland
 - CHD morbidity and mortality in, smokers vs. nonsmokers, 95
 - cigarette smoke effects on mice lung and kidney tissue in, 344
 - cigarette smoke inhalation effects on mice respiratory tract, 351
 - lung neoplasm incidence in cigar and pipe smokers of rural, 244
 - retrospective smoking study of methods for lung neoplasms in, 325
 - serum lipid differences in smokers vs. nonsmokers of, 100
- Tachycardia
 - development in dogs induced by nicotine, 57
- TAO
 - see* Thromboangiitis obliterans
- Tars, tobacco
 - carcinogenicity on animal skin, 238
 - carcinogenic properties from cigarette smoke, 11, 264, 265
 - content in cigarettes, relationship to lung neoplasm development, 275, 276
 - sarcoma induction in rats following instillation, 346
 - skin painting with, carcinoma induction from, 337-342
- Telephone company employees
 - see* Occupations
- Teratogenesis
 - maternal smoking implications in, 407
 - in mice embryos, nicotine effects on, 411
- Tetraethylammonium chloride
 - blockage of nicotine cardiac stimulation by, 57
- Textile workers
 - see* Occupations
- Thromboangiitis obliterans
 - definition, 73
 - remission of, cessation of smoking effects, 74
- Thrombosis
 - smoking effects on, 66, 130-132
- Tissues
 - cultures of, cigarette smoke effects on cell growth and reproduction, 267, 343-345
 - hypoxia of, carbon monoxide effects on, 61
- Tobacco
 - see also* all forms, e.g. Cigarettes, etc.
 - chewing of, relationship to lip and oral cavity neoplasms, 361-363, 365-366
 - leaves, presence of potassium-40 in, 266
 - Tobacco amblyopia
 - see* Amblyopia
 - Tobacco tars
 - see* Tars, tobacco
 - Tongue
 - hamster, C-14 labeled particulate deposition in, 281-282
 - Toxemia
 - preeclamptic, incidence in smoking and nonsmoking mothers, 404, 407
 - Trachea
 - hamster, C-14 labeled particulate deposition in, 281-282
 - Transportation employees
 - see* Occupations
 - Triglycerides
 - CHD incidence relationship to, 65
 - smokers vs. nonsmokers, 99-100, 102
 - Trypsin
 - see* Anti-trypsin, alpha₁
 - Tryptophan metabolism
 - alterations by smoking, 297
 - alteration in urinary tract neoplasms by smoking, 13
 - carcinogenicity in mice bladders, 296
 - relation of excretion in smokers and nonsmokers, 297
 - Tuberculosis
 - relationship of smokers vs. nonsmokers to, 172, 226-228
 - Tumorigenic agents
 - see* Carcinogens
 - Twins
 - angina pectoris development in, smoking effects on, 50-51
 - genetic studies of smoking effects on, 49-52
 - smoking effects on mortality and morbidity in, 51
 - Ulcers
 - see* Peptic ulcers
 - United Kingdom
 - bladder neoplasms in, methods in retrospective studies of smoking and, 382-384
 - blood pressure differences in smokers vs. nonsmokers in, 103, 104
 - British Perinatal Mortality Survey of, 390, 395, 404, 415
 - cigarette smoke effects on human fetal lung and mice trachea, 344
 - cigarette smoke effects on human pulmonary function, 168, 169
 - cigarette smoke effects on mice respiratory tract, 352
 - cigarette smoke implantation effects on rat tracheobronchial tree in, 346-347
 - comparison of abortions, stillbirths and neonatal deaths in smoking and nonsmoking mothers, 406
 - COPD morbidity in smokers in, 195-197, 203, 204
 - effect of cigarette smoke on animal ciliary function in, 221
 - human experimental data on smoking and pregnancy, 408
 - kidney and bladder neoplasms in

smokers in, 294
 lung cancer mortality in males in England and Wales, 240
 maternal smoking and infant weight in, 397, 399
 methods used in smoking study and human pregnancy, 391, 394-395
 mortality from cerebrovascular disease related to smoking in, 68
 mortality rates from COPD in, lack of increase, 140
 mortality ratios from esophageal neoplasms in, 290
 mortality ratios from laryngeal neoplasms in, 278
 mortality ratios from peptic ulcer in smokers and nonsmokers in, 424
 occupational exposure and smoking relationships to COPD in 218-219
 peptic ulcer in, methods and results of retrospective and cross section studies of smoking and, 425-428
 physicians in, decline in cigarette smoking rates, 48
 physicians in, mortality from lung neoplasms in smokers and nonsmokers, 241
 pulmonary function in, cigarette smoke effects on, 168
 relationships of lung neoplasms to smoking, air pollution, and residence in, 253-254
 relationship of smoking tuberculosis in, 226
 retrospective smoking study of methods for lung neoplasms in, 324, 326
 serum lipid differences in smokers vs. nonsmokers in, 101, 102
 smoking and nicotine effects on animal cardiovascular function in, 107
 smoking and nicotine effects on human blood lipids in, 126
 smoking and nicotine effects on human cardiovascular system in, 115
 smoking relationships to thrombosis in, 131
 United States
 acute effect of cigarette smoke on human pulmonary function in, 166-167, 169
 atherosclerosis autopsy studies in, 53-55
 bladder neoplasms in, methods and results in retrospective studies of smoking and, 381-384
 blood pressure differences in smokers vs. nonsmokers in, 103-104
 CHD mortality and morbidity in smokers vs. nonsmokers in, 30-35, 37, 93-94
 comparison of abortions, stillbirth and neonatal death in smoking and non-smoking mothers, 405-406
 cigarette smoke effects on animal tissues in, 343-345
 cigarette smoke effects pulmonary surfactants and surface tension, 172, 225
 cigarette smoke implantation effects on animals tracheobronchial tree, 346-348
 cigarette smoke inhalation effects on animal respiratory tracts, 349-350, 352, 354
 COPD morbidity in smokers in, 195, 196, 198-200, 201-202, 205
 effects of cigarette smoke on animal ciliary function in, 221-224
 esophageal neoplasms in, retrospective studies of tobacco use, 378
 esophageal neoplasm mortality in, in 1967, 289
 human experimental data on smoking and pregnancy in, 408-410
 human pulmonary function following cessation of smoking in, 149
 kidney and bladder neoplasms in smokers in, 293-295
 laryngeal neoplasm incidence in 1967, 277
 laryngeal neoplasm in, relationships to tobacco use, 278-279, 354-355
 lung neoplasm mortality in smokers and nonsmokers in, 240-243
 maternal smoking and infant weight, 397-399
 methods used in smoking study and human pregnancy, 391-395
 mortality from aortic aneurysm related to smoking in, 71
 mortality from cerebrovascular disease related to smoking, 68-70
 mortality from lung neoplasms expected in 1970, 237, 239
 mortality rates for bladder neoplasms in 1967, 293
 mortality rates for COPD, increase of 139-140
 mortality rates for kidney neoplasms in 1967, 296
 mortality rates for lung neoplasms in 1939 vs. 1967, 239
 mortality ratios for COPD, 142-145
 mortality ratios for esophageal neoplasms in, 290-294
 mortality ratios for laryngeal neoplasms, 278-279
 mortality ratios for pancreatic neoplasms in smokers and nonsmokers in, 298
 mortality ratios for peptic ulcer in smokers and nonsmokers in, 424
 occupational exposure and smoking relationships to COPD in, 218-219
 oral neoplasm incidence in, estimated for 1970, 284
 peptic ulcer mortality in 1967 in, 423
 peptic ulcer in, methods and results for retrospective and cross section studies of smoking and, 425, 426-428
 polonium-210 levels in lungs of smokers in, 335-336
 populations of, COPD development in, 10
 relationship of human pulmonary histology and smoking in, 155-157
 relationship of tobacco use and lip neoplasms, 361-365, 367
 relationship of tobacco use and neoplasms of oral cavity, 361-365, 367
 relationship of lung neoplasm to smoking, air pollution, and residence in, 253-254

relationship of smoking to infectious respiratory disease in, 227-229
 retrospective smoking study methods for lung neoplasms in, 323-328
 serum lipid differences in smokers vs. nonsmokers in, 98, 100, 101
 smoking relationship to thrombosis in, 130, 131
 smoking and nicotine effects on animal cardiovascular function in, 107-112
 smoking and nicotine effects on human blood lipids, 123-126
 smoking or nicotine effects on human catecholamine levels, 119
 smoking and nicotine effects on human cardiovascular system, 113-114, 116, 117-119
 smoking and nicotine effects on human peripheral vascular system, 133-134
 surveys of cigarette smoking in, 6
 tracheobronchial tree changes in smokers and nonsmokers in, 259-263

Uranium miners
see Occupations

Urban environment
 contribution to lung cancer mortality, 11
 relationship of lung neoplasms, smoking, air pollution to, 252-255

Urban populations
 lung neoplasms in, suspected etiology of increased, 276

Urinary bladder
see Bladder

Uterus
 cigarette smoking effects on gravidic, 408

Utility Company employees
see Occupations

Vascular system
see also Blood circulation, cardiovascular system, cerebrovascular system, thromboangiitis obliterans
 peripheral, smoking and nicotine effect on, 9, 72-73, 75, 133-134

Venezuela
 maternal smoking and infant weight in, 450
 methods used in smoking study and human pregnancy, 445

Ventricular fibrillation
 death from, nicotine effects on, 36

Ventilatory function tests
see Respiratory system

Veterans
see Occupations

Virus
 influenza, cigarette smoke effects on resistance of mice with, 173
 influenza, nitrogen oxide effects on squirrel monkey resistance to, 173

Vitamin deficiency
 relationship to tobacco amblyopia

Xenon
 radioactive, regional pulmonary function using, 147