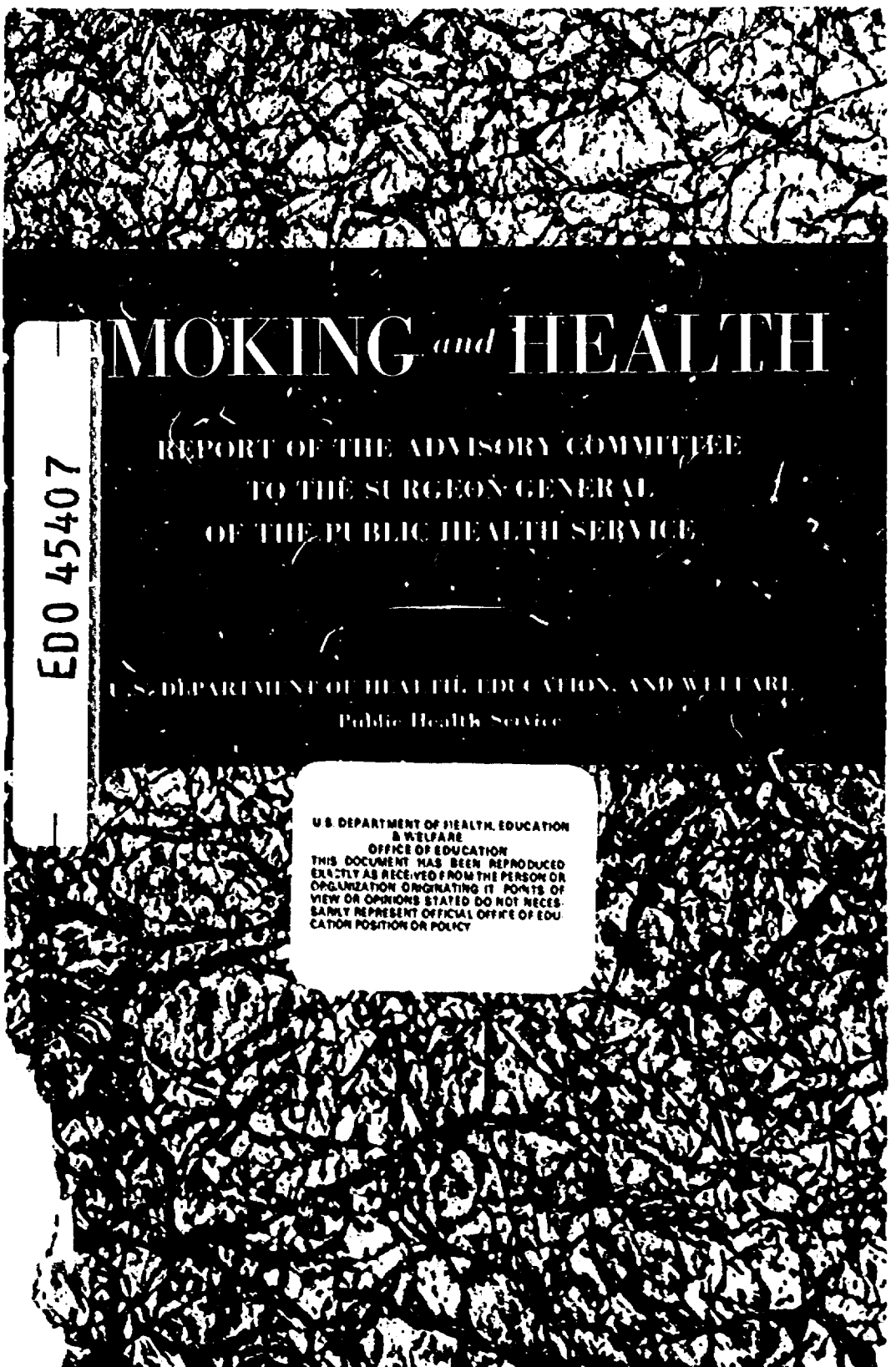
DOCUMENT RESUME

ED 045 407 SE 010 136

TITLE	Smoking and Health, Report of the Advisory Committee to the Surgeon General of the Public Health Service.
INSTITUTION	Public Health Service (DHEW), Washington, D.C.
REPORT NO	PHS-Pub-1103
PUB DATE	64
NOTE	390p.
AVAILABLE FROM	Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402 (Cat. No. FS 2.2:SM 7/2, $1.25)
EDRS PRICE	EDRS Price MF-$1.50 HC Not Available from EDPS.
DESCRIPTORS	Environmental Education, Health, *Health Education, *Medical Research, Physiology, *Research Reviews (Publications), *Smoking, Stimulants, *Tobacco

ABSTRACT

Reported is a review of the literature regarding the relationships of the use of tobacco, especially the smoking of cigarettes, to the health of men and women, primarily in the United States. Topical divisions of the report are: Consumption of Tobacco Products in the United States; Chemical and Physical Characteristics of Tobacco and Tobacco Smoke; Pharmacology and Toxicology of Nicotine; Mortality; Cancer; Non-neoplastic Respiratory Diseases: Cardiovascular Diseases; Other Conditions; Characterization of the Tobacco Habit and Beneficial Effects of Smoking: Psycho-social Aspects of Smoking; and Morphological Constitution of Smokers. Included are summaries and conclusions of the analyses. (BP)



SMOKING and HEALTH

REPORT OF THE ADVISORY COMMITTEE
TO THE SURGEON GENERAL
OF THE PUBLIC HEALTH SERVICE

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

SMOKING *and* HEALTH

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Public Health Service Publication No. 1103

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C., 20402 - Price $1.25

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Foreword

Since the turn of the century, scientists have become increasingly interested in the effects of tobacco on health. Only within the past few decades, however, has a broad experimental and clinical approach to the subject been manifest; within this period the most extensive and definitive studies have been undertaken since 1950.

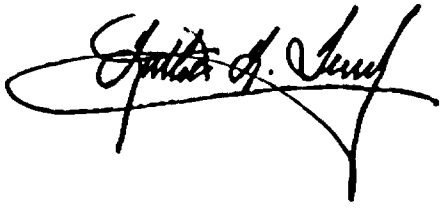
Few medical questions have stirred such public interest or created more scientific debate than the tobacco-health controversy. The interrelationships of smoking and health undoubtedly are complex. The subject does not lend itself to easy answers. Nevertheless, it has been increasingly apparent that answers must be found.

As the principal Federal agency concerned broadly with the health of the American people, the Public Health Service has been conscious of its deep responsibility for seeking these answers. As steps in that direction it has seemed necessary to determine, as precisely as possible, the direction of scientific evidence and to act in accordance with that evidence for the benefit of the people of the United States. In 1959, the Public Health Service assessed the then available evidence linking smoking with health and made its findings known to the professions and the public. The Service's review of the evidence and its statement at that time was largely focussed on the relationship of cigarette smoking to lung cancer. Since 1959 much additional data has accumulated on the whole subject.

Accordingly, I appointed a committee, drawn from all the pertinent scientific disciplines, to review and evaluate both this new and older data and, if possible, to reach some definitive conclusions on the relationship between smoking and health in general. The results of the Committee's study and evaluation are contained in this Report.

I pledge that the Public Health Service will undertake a prompt and thorough review of the Report to determine what action may be appropriate and necessary. I am confident that other Federal agencies and nonofficial agencies will do the same.

The Committee's assignment has been most difficult. The subject is complicated and the pressures of time on eminent men busy with many other duties has been great. I am aware of the difficulty in writing an involved technical report requiring evaluations and judgments from many different professional and technical points of view. The completion of the Committee's task has required the exercise of great professional skill and dedication of the highest order. I acknowledge a profound debt of gratitude to the Committee, the many consultants who have given their assistance, and the members of the staff. In doing so, I extend thanks not only for the Service but for the Nation as a whole.



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During this study the Advisory Committee on Smoking and Health has had the constant support of individuals, groups and institutions throughout a broad range of professional and technical occupations. In many cases the contributions of these individuals involved considerable personal, professional or financial sacrifice. In every case the contributions lessened the burden of the Committee and increased the authority and completeness of the Report. In this space it is impossible to assign priorities or special emphasis to individual contributions or contributors. The Committee, however, does acknowledge with gratitude and deep appreciation—and with sincere apologies to any individual inadvertently omitted—the substantial cooperation and assistance of the following:

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PART I

Introduction, Summaries, and Conclusions

Chapter 1

Introduction

Chapter 1

Realizing that for the convenience of all types of serious readers it would be desirable to simplify language, condense chapters and bring opinions to the forefront, the Committee offers Part I as such a presentation. This Part includes: (a) an introduction comprising, among other items, a chronology especially pertinent to the subject of this study and to the establishment and activities of the Committee, (b) a short account of how the study was conducted, (c) the chief criteria used in making judgments, and (d) a brief overview of the entire Report.

HISTORICAL NOTES AND CHRONOLOGY

In the early part of the 16th century, soon after the introduction of tobacco into Spain and England by explorers returning from the New World, controversy developed from differing opinions as to the effects of the human use of the leaf and products derived from it by combustion or other means. Pipe-smoking, chewing, and snuffing of tobacco were praised for pleasurable and reputed medicinal actions. At the same time, smoking was condemned as a foul-smelling, loathsome custom, harmful to the brain and lungs. The chief question was then as it is now: is the use of tobacco bad or good for health, or devoid of effects on health? Parallel with the increasing production and use of tobacco, especially with the constantly increasing smoking of cigarettes, the controversy has become more and more intense. Scientific attack upon the problems has increased proportionately. The design, scope and penetration of studies have improved, and the yield of significant results has been abundant.

The modern period of investigation of smoking and health is included within the past sixty-three years. In 1900 an increase in cancer of the lung was noted particularly by vital statisticians, and their data are usually taken as the starting point for studies on the possible relationship of smoking and other uses of tobacco to cancer of the lung and of certain other organs, to diseases of the heart and blood vessels (cardiovascular diseases in general; coronary artery disease in particular), and to the non-cancerous (non-neoplastic) diseases of the lower respiratory tract (especially chronic bronchitis and emphysema). The next important basic date for starting comparisons is 1930, when the definite trends in mortality and disease-incidence considered in this Report became more conspicuous. Since then a great variety of investigations have been carried out. Many of the chemical compounds in tobacco and in tobacco smoke have been isolated and tested. Numerous experimental studies in lower animals have been made by exposing them to smoke and to tars, gases and various constituents in tobacco and tobacco smoke. It is not feasible to submit human beings to

experiments that might produce cancers or other serious damage, or to expose them to possibly noxious agents over the prolonged periods under strictly controlled conditions that would be necessary for a valid test. Therefore, the main evidence of the effects of smoking and other uses of tobacco upon the health of human beings has been secured through clinical and pathological observations of conditions occurring in men, women and children in the course of their lives, and by the application of epidemiological and statistical methods by which a vast array of information has been assembled and analyzed.

Among the epidemiological methods which have been used in attempts to determine whether smoking and other uses of tobacco affect the health of man, two types have been particularly useful and have furnished information of the greatest value for the work of this Committee. These are (1) *retrospective studies* which deal with data from the personal histories and medical and mortality records of human individuals in groups; and (2) *prospective studies*, in which men and women are chosen randomly or from some special group, such as a profession, and are followed from the time of their entry into the study for an indefinite period, or until they die or are lost on account of other events.

Since 1939 there have been 29 retrospective studies of lung cancer alone which have varying degrees of completeness and validity. Following the publication of several notable retrospective studies in the years 1952–1956, the medical evidence tending to link cigarette smoking to cancer of the lung received particularly widespread attention. At this time, also, the critical counterattack upon retrospective studies and upon conclusions drawn from them was launched by unconvinced individuals and groups. The same types of criticism and skepticism have been, and are, marshalled against the methods, findings, and conclusions of the later prospective studies. They will be discussed further in Chapter 3, Criteria for Judgment, and in other chapters, especially Chapter 8, Mortality, and Chapter 9, Cancer.

During the decade 1950–1960, at various dates, statements based upon the accumulated evidence were issued by a number of organizations. These included the British Medical Research Council; the cancer societies of Denmark, Norway, Sweden, Finland, and the Netherlands; the American Cancer Society; the American Heart Association; the Joint Tuberculosis Council of Great Britain; and the Canadian National Department of Health and Welfare. The consensus, publicly declared, was that smoking is an important health hazard, particularly with respect to lung cancer and cardiovascular disease.

Early in 1954, the Tobacco Industry Research Committee (T.I.R.C.) was established by representatives of tobacco manufacturers, growers, and warehousemen to sponsor a program of research into questions of tobacco use and health. Since then, under a Scientific Director and a Scientific Advisory Board composed of nine scientists who maintain their respective institutional affiliations, the Tobacco Industry Research Committee has conducted a grants-in-aid program, collected information, and issued reports.

The U.S. Public Health Service first became officially engaged in an appraisal of the available data on smoking and health in June, 1956, when, under the instigation of the Surgeon General, a scientific Study Group on

the subject was established jointly by the National Cancer Institute, the National Heart Institute, the American Cancer Society, and the American Heart Association. After appraising 16 independent studies carried on in five countries over a period of 18 years, this group concluded that there is a causal relationship between excessive smoking of cigarettes and lung cancer.

Impressed by the report of the Study Committee and by other new evidence, Surgeon General Leroy E. Burney issued a statement on July 12, 1957, reviewing the matter and declaring that: "The Public Health Service feels the weight of the evidence is increasingly pointing in one direction; that excessive smoking is one of the causative factors in lung cancer." Again, in a special article entitled "Smoking and Lung Cancer—A Statement of the Public Health Service," published in the Journal of the American Medical Association on November 28, 1959, Surgeon General Burney referred to his statement issued in 1957 and reiterated the belief of the Public Health Service that: "The weight of evidence at present implicates smoking as the principal factor in the increased incidence of lung cancer," and that: "Cigarette smoking particularly is associated with an increased chance of developing lung cancer." These quotations state the position of the Public Health Service taken in 1957 and 1959 on the question of smoking and health. That position has not changed in the succeeding years, during which several units of the Service conducted extensive investigations on smoking and air pollution, and the Service maintained a constant scrutiny of reports and publications in this field.

ESTABLISHMENT OF THE COMMITTEE

The immediate antecedents of the establishment of the Surgeon General's Advisory Committee on Smoking and Health began in mid-1961. On June 1 of that year, a letter was sent to the President of the United States, signed by the presidents of the American Cancer Society, the American Public Health Association, the American Heart Association, and the National Tuberculosis Association. It urged the formation of a Presidential commission to study the "widespread implications of the tobacco problem."

On January 4, 1962, representatives of the various organizations met with Surgeon General Luther L. Terry, who shortly thereafter proposed to the Secretary of Health, Education, and Welfare the formation of an advisory committee composed of "outstanding experts who would assess available knowledge in this area [smoking vs. health] and make appropriate recommendations . . ."

On April 16, the Surgeon General sent a more detailed proposal to the Secretary for the formation of the advisory group, calling for re-evaluation of the Public Health Service position taken by Dr. Burney in the Journal of the American Medical Association. Dr. Terry felt the need for a new look at the Service's position in the light of a number of significant developments since 1959 which emphasized the need for further action. He listed these as:

1. New studies indicating that smoking has major adverse health effects.

2. Representations from national voluntary health agencies for action on the part of the Service.

3. The recent study and report of the Royal College of Physicians of London.

4. Action of the Italian Government to forbid cigarette and tobacco advertising; curtailed advertising of cigarettes by Britain's major tobacco companies on TV; and a similar decision on the part of the Danish tobacco industry.

5. A proposal by Senator Maurine Neuberger that Congress create a commission to investigate the health effects of smoking.

6. A request for technical guidance by the Service from the Federal Trade Commission on labeling and advertising of tobacco products.

7. Evidence that medical opinion has shifted significantly against smoking.

The recent study and report cited by Surgeon General Terry was the highly important volume: "Smoking and Health—Summary and Report of the Royal College of Physicians of London on Smoking in Relation to Cancer of the Lung and Other Diseases." The Committee of the Royal College of Physicians dealing with these matters had been at its work of appraisal of data since April 1959. Its main conclusions, issued early in 1962, were: "Cigarette smoking is a cause of lung cancer and bronchitis, and probably contributes to the development of coronary heart disease and various other less common diseases. It delays healing of gastric and duodenal ulcers."

On June 7, 1962, the Surgeon General announced that he was establishing an expert committee to undertake a comprehensive review of all data on smoking and health. The President later in the same day at his press conference acknowledged the Surgeon General's action and approved it.

On July 24, 1962, the Surgeon General met with representatives of the American Cancer Society, the American College of Chest Physicians, the American Heart Association, the American Medical Association, the Tobacco Institute, Inc., the Food and Drug Administration, the National Tuberculosis Association, the Federal Trade Commission, and the President's Office of Science and Technology. At this meeting, it was agreed that the proposed work should be undertaken in two consecutive phases, as follows:

Phase I—An objective assessment of the nature and magnitude of the health hazard, to be made by an expert scientific advisory committee which would review critically all available data but would not conduct new research. This committee would produce and submit to the Surgeon General a technical report containing evaluations and conclusions.

Phase II—Recommendations for actions were not to be a part of the Phase I committee's responsibility. No decisions on how Phase II would be conducted were to be made until the Phase I report was available. It was recognized that different competencies would be needed in the second phase and that many possible recommendations for action would extend beyond the health field and into the purview and competence of other Federal agencies.

The participants in the meeting of July 27 compiled a list of more than 150 scientists and physicians working in the fields of biology and medicine,

with interests and competence in the broad range of medical sciences and with capacity to evaluate the elements and factors in the complex relationship between tobacco smoking and health. During the next month, these lists were screened by the representatives of organizations present at the July 27 meeting. Any organization could veto any of the names on the list, no reasons being required. Particular care was taken to eliminate the names of any persons who had taken a public position on the questions at issue. From the final list of names the Surgeon General selected ten men who agreed to serve on the Phase I committee, which was named *The Surgeon General's Advisory Committee on Smoking and Health.* The committee members, their positions, and their fields of competence are:

Stanhope Bayne-Jones, M.D., LL.d., (Retired), Former Dean, Yale School of Medicine (1935–40), former President, Joint Administrative Board, Cornell University, New York Hospital Medical Center (1947–52); former President, Society of American Bacteriologists (1929), and American Society of Pathology and Bacteriology (1940). Field: Nature and Causation of Disease in Human Populations.

Dr. Bayne-Jones served also as a special consultant to the Committee staff.

Walter J. Burdette, M.D., Ph. D., Head of Department of Surgery, University of Utah School of Medicine, Salt Lake City. Fields: Clinical & Experimental Surgery; Genetics.

William G. Cochran, M.A., Professor of Statistics, Harvard University. Field: Mathematical Statistics, with Special Application to Biological Problems.

Emmanuel Farber, M.D., Ph. D., Chairman, Department of Pathology, University of Pittsburgh. Field: Experimental and Clinical Pathology.

Louis F. Fieser, Ph. D., Sheldon Emory, Professor of Organic Chemistry, Harvard University. Field: Chemistry of Carcinogenic Hydrocarbons.

Jacob Furth, M.D., Professor of Pathology, Columbia University, and Director of Pathology Laboratories, Francis Delafield Hospital, New York, N.Y. Field: Cancer Biology.

John B. Hickam, M.D., Chairman, Department of Internal Medicine, University of Indiana, Indianapolis. Fields: Internal Medicine, Physiology of Cardiopulmonary Disease.

Charles LeMaistre, M.D., Professor of Internal Medicine, The University of Texas Southwestern Medical School, and Medical Director, Woodlawn Hospital, Dallas, Texas. Fields: Internal Medicine, Pulmonary Diseases, Preventive Medicine.

Leonard M. Schuman, M.D., Professor of Epidemiology, University of Minnesota School of Public Health, Minneapolis. Field: Health and Its Relationship to the Total Environment.

Maurice H. Seevers, M.D., Ph. D., Chairman, Department of Pharmacology, University of Michigan, Ann Arbor. Field: Pharmacology of Anesthesia and Habit-Forming Drugs.

Chairman: Luther L. Terry, M.D., Surgeon General of the United States Public Health Service.

Vice-Chairman: James M. Hundley, M.D., Assistant Surgeon General for Operations, United States Public Health Service.

Staff Director	*Medical Coordinator*
Eugene H. Guthrie, M.D., M.P.H. Public Health Service	Peter V. V. Hamill, M.D., M.P.H. Public Health Service

Chapter 2

Conduct of the Study

Chapter 2

CONDUCT OF THE STUDY

The work of the Surgeon General's Advisory Committee on Smoking and Health was undertaken, organized, and pursued with independence, a deep sense of responsibility, and with full appreciation of the national importance of the task. The Committee's constant desire was to carry out in its own way, with the best obtainable advice and cooperation from experts outside its membership, a thorough and objective review and evaluation of available information about the effects of the use of various forms of tobacco upon the health of human beings. It desired that the Report of its studies and judgments should be unquestionably the product of its labors and its authorship. With an enormous amount of assistance from 155 consultants, from members and associates of the supporting staff, and from several organizations and institutions, the Committee feels that a document of adequate scope, integrity, and individuality has been produced. It is emphasized, however, that the content and judgments of the Report are the sole responsibility of the Committee.

At the outset, the Surgeon General emphasized his respect for the freedom of the Committee to proceed with the study and to report as it saw fit, and he pledged all support possible from the United States Public Health Service. The Service, represented chiefly by his office, the National Institutes of Health, the National Library of Medicine, the Bureau of State Services, and the National Center for Health Statistics, furnished the able and devoted personnel that constituted the staff at the Committee's headquarters in Washington, and provided an extraordinary variety and volume of supplies, facilities and resources. In addition, the necessary financial support was made available by the Service.

It is the purpose of this section to present an outline of the important features of the manner in which the Committee conducted its study and composed this Report. A retrospective outline of procedures and events tends to convey an appearance of orderliness that did not pertain at all times. A plan was adopted at the first meeting of the Committee on November 9–10, 1962, but this had to be modified from time to time as new lines of inquiry led into unanticipated explorations. At first an encyclopedic approach was considered to deal with all aspects of the use of tobacco and the resulting effects, with all relevant aspects of air pollution, and all pertinent characteristics of the external and internal environments and make-up of human beings. It was soon found to be impracticable to attempt to do all of this in any reasonable length of time, and certainly not under the urgencies of the existing situation. The final plan was to give particular attention to the cores of problems of the relationship of uses of tobacco, especially the smoking of cigarettes, to the health of men and women, primarily in the United States, and

to deal with the material from both a general viewpoint and on the basis of disease categories.

As may be seen in a glance at the Table of Contents of this Report, the main topical divisions of the study were:

- Tobacco and tobacco smoke, chemical and physical characteristics (Chapter 6).
- Nicotine, pharmacology and toxicology (Chapter 7).
- Mortality, general and specific, according to age, sex, disease, and smoking habits, and other factors (Chapter 8).
- Cancer of the lungs and other organs; carcinogenesis; pathology, and epidemiology (Chapter 9).
- Non-neoplastic diseases of the respiratory tract, particularly chronic bronchitis and emphysema, with some consideration of the effects of air pollution (Chapter 10).
- Cardiovascular diseases, particularly coronary artery diseases (Chapter 11).
- Other conditions, a miscellany including gastric and duodenal ulcer, perinatal disorders, tobacco amblyopia, accidents (Chapter 12).
- Characterization of the tobacco habit and beneficial effects of tobacco (Chapter 13).
- Psycho-social aspects of smoking (Chapter 14).
- Morphological constitution of smokers (Chapter 15).

As the primary duty of the Committee was to assess information about smoking and health, a major general requirement was that of making the information available. That requirement was met in three ways. The first and most important was the bibliographic service provided by the National Library of Medicine. As the annotated monograph by Larson, Haag, and Silvette—compiled from more than 6,000 articles published in some 1,200 journals up to and largely into 1959—was available as a basic reference source, the National Library of Medicine was requested to compile a bibliography (by author and by subject) covering the world literature from 1958 to the present. In compliance with this request, the National Library of Medicine furnished the Committee bibliographies containing approximately 1100 titles. Fortunately, the Committee staff was housed in the National Library of Medicine on the grounds of the National Institutes of Health, and through this location had ready access to books and periodicals, as well as to scientists working in its field of interests. Modern apparatus for photo-reproduction of articles was used constantly to provide copies needed for study by members of the Committee. In addition, the members drew upon the libraries and bibliographic services of those institutions in which they held academic positions. A considerable volume of copies of reports and a number of special articles were received from a variety of additional sources.

All of the major companies manufacturing cigarettes and other tobacco products were invited to submit statements and any information pertinent to the inquiry. The replies which were received were taken into consideration by the Committee.

Through a system of contracts with individuals competent in certain fields, special reports were prepared for the use of the Committee. Through these

sources much valuable information was obtained; some of it new and hitherto unpublished.

In addition to the special reports prepared under contracts, many conferences, seminar-like meetings, consultations, visits and correspondence made available to the Committee a large amount of material and a considerable amount of well-informed and well-reasoned opinion and advice.

To deal in depth and discrimination with the topics listed above, the Committee at its first meeting formed subcommittees with much overlapping in membership. These subcommittees were the main forces engaged in collection, analysis, and evaluation of data from published reports, contractual reports, discussions at conferences, and from some new prospective studies reprogrammed and carried out generously at the request of the Committee. These will be acknowledged more fully elsewhere in this Report. The first formulations of conclusions were made by these subcommittees, and these were submitted to the full Committee for revision and adoption after debate.

At the beginning, and until the Committee began to meet routinely in executive session, it had the advantage of attendance at its meetings of observers from other Federal agencies. There were representatives from the following agencies: Executive Office of the President of the United States, Federal Trade Commission, Department of Commerce, Department of Agriculture, and the Food and Drug Administration. Serving as more than observers and reporters to their agencies, when they were present or by written communication, they supplied the Committee with much useful information.

There were an uncounted number of meetings of subcommittees and other lesser gatherings. Between November 1962 and December 1963, the full Committee held nine sessions each lasting from two to four days in Washington or Bethesda. The main matters considered at the meetings in October, November, and December 1963 were the review and revision of chapters, critical scrutiny of conclusions, and the innumerable details of the composition and editing of this comprehensive Report.

Chapter 3

Criteria for Judgment

Chapter 3

CRITERIA FOR JUDGMENT

In making critical appraisals of data and interpretations and in formulating its own conclusions, the Surgeon General's Advisory Committee on Smoking and Health—its individual members and its subcommittees and the Committee as a whole—made decisions or judgments at three levels. These levels were:

I. Judgment as to the validity of a publication or report. Entering into the making of this judgment were such elements as estimates of the competence and training of the investigator, the degree of freedom from bias, design and scope of the investigation, adequacy of facilities and resources, adequacy of controls.

II. Judgment as to the validity of the interpretations placed by investigators upon their observations and data, and as to the logic and justification of their conclusions.

III. Judgments necessary for the formulation of conclusions within the Committee.

The primary reviews, analyses and evaluations of publications and unpublished reports containing data, interpretations and conclusions of authors were made by individual members of the Committee and, in some instances, by consultants. Their statements were next reviewed and evaluated by a subcommittee. This was followed at an appropriate time by the Committee's critical consideration of a subcommittee's report, and by decisions as to the selection of material for inclusion in the drafts of the Report, together with drafts of the conclusions submitted by subcommittees. Finally, after repeated critical reviews of drafts of chapters, conclusions were formulated and adopted by the whole Committee, setting forth the considered judgment of the Committee.

It is not the intention of this section to present an essay on decision-making. Nor does it seem necessary to describe in detail the criteria used for making scientific judgments at each of the three levels mentioned above. All members of the Committee were schooled in the high standards and criteria implicit in making scientific assessments; if any member lacked even a small part of such schooling he received it in good measure from the strenuous debates that took place at consultations and at meetings of the subcommittees and the whole Committee.

Criteria of the Epidemiologic Method

It is advisable, however, to discuss briefly certain criteria which, although applicable to all judgments involved in this Report, were especially significant for judgments based upon the epidemiologic method. In this inquiry the

epidemiologic method was used extensively in the assessment of causal factors in the relationship of smoking to health among human beings upon whom direct experimentation could not be imposed. Clinical, pathological and experimental evidence was thoroughly considered and often served to suggest an hypothesis or confirm or contradict other findings. When coupled with the other data, results from the epidemiologic studies can provide the basis upon which judgments of causality may be made.

In carrying out studies through the use of this epidemiologic method, many factors, variables, and results of investigations must be considered to determine first whether an association actually exists between an attribute or agent and a disease. Judgment on this point is based upon indirect and direct measures of the suggested association. If it be shown that an association exists, then the question is asked: "Does the association have a causal significance?"

Statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability. To judge or evaluate the causal significance of the association between the attribute or agent and the disease, or effect upon health, a number of criteria must be utilized, no one of which is an all-sufficient basis for judgment. These criteria include:

a) The consistency of the association
b) The strength of the association
c) The specificity of the association
d) The temporal relationship of the association
e) The coherence of the association

These criteria were utilized in various sections of this Report. The most extensive and illuminating account of their utilization is to be found in Chapter 9 in the section entitled "Evaluation of the Association Between Smoking and Lung Cancer".

Causality

Various meanings and conceptions of the term *cause* were discussed vigorously at a number of meetings of the Committee and its subcommittees. These debates took place usually after data and reports had been studied and evaluated, and at the times when critical scrutiny was being given to conclusions and to the wording of conclusive statements. In addition, thoughts about causality in the realm of this inquiry were constantly and inevitably aroused in the minds of the members because they were preoccupied with the subject of their investigation—"Smoking and Health."

Without summarizing the more important concepts of causality that have determined human attitudes and actions from the days even before Aristotle, through the continuing era of observation and experiment, to the statistical certainties of the present atomic age, the point of view of the Committee with regard to causality and to the language used in this respect in this report may be stated briefly as follows:

1. The situation of smoking in relation to the health of mankind includes a host (variable man) and a complex agent (tobacco and its products, partic-

ularly those formed by combustion in smoking). The probe of this inquiry is into the effect, or non-effect, of components of the agent upon the tissues, organs, and various qualities of the host which might: a) improve his well-being, b) let him proceed normally, or c) injure his health in one way or another. To obtain information on these points the Committee did its best, with extensive aid, to examine all available sources of information in publications and reports and through consultation with well informed persons.

2. When a relationship or an association between smoking, or other uses of tobacco, and some condition in the host was noted, the significance of the association was assessed.

3. The characterization of the assessment called for a specific term. The chief terms considered were "factor," "determinant," and "cause." The Committee agreed that while a factor could be a source of variation, not all sources of variation are causes. It is recognized that often the coexistence of several factors is required for the occurrence of a disease, and that one of the factors may play a determinant role, i.e., without it the other factors (as genetic susceptibility) are impotent. Hormones in breast cancer can play such a determinant role. The word *cause* is the one in general usage in connection with matters considered in this study, and it is capable of conveying the notion of a significant, effectual, relationship between an agent and an associated disorder or disease in the host.

4. It should be said at once, however, that no member of this Committee used the word "cause" in an absolute sense in the area of this study. Although various disciplines and fields of scientific knowledge were represented among the membership, all members shared a common conception of the multiple etiology of biological processes. No member was so naive as to insist upon mono-etiology in pathological processes or in vital phenomena. All were thoroughly aware of the fact that there are series of events in occurrences and developments in these fields, and that the end results are the net effect of many actions and counteractions.

5. Granted that these complexities were recognized, it is to be noted clearly that the Committee's considered decision to use the words "a cause," or "a major cause," or "a significant cause," or "a causal association" in certain conclusions about smoking and health affirms their conviction.

Chapter 4

Summaries and Conclusions

Contents

List of Table

Chapter 4

This chapter is presented in two sections. Section A contains background information, the gist of the Committee's findings and conclusions on tobacco and health, and an assessment of the nature and magnitude of the health hazard. Section B presents all formal conclusions adopted by the Committee and selected comments abridged from the detailed Summaries that appear in each chapter of Part II of the Report. The full scope and depth of the Committee's inquiry may be comprehended only by study of the complete Report.

A. BACKGROUND AND HIGHLIGHTS

In previous studies, the use of tobacco, especially cigarette smoking, has been causally linked to several diseases. Such use has been associated with increased deaths from lung cancer and other diseases, notably coronary artery disease, chronic bronchitis, and emphysema. These widely reported findings, which have been the cause of much public concern over the past decade, have been accepted in many countries by official health agencies, medical associations, and voluntary health organizations.

The potential hazard is great because these diseases are major causes of death and disability. In 1962, over 500,000 people in the United States died of arteriosclerotic heart disease (principally coronary artery disease), 41,000 died of lung cancer, and 15,000 died of bronchitis and emphysema.

The numbers of deaths in some important disease categories that have been reported to have a relationship with tobacco use are shown in Table 1. This table presents one aspect of the size of the potential hazard; the degree of association with the use of tobacco will be discussed later.

Another cause for concern is that deaths from some of these diseases have been increasing with great rapidity over the past few decades.

Lung cancer deaths, less than 3,000 in 1930, increased to 18,000 in 1950. In the short period since 1955, deaths from lung cancer rose from less than 27,000 to the 1962 total of 41,000. This extraordinary rise has not been recorded for cancer of any other site. While part of the rising trend for lung cancer is attributable to improvements in diagnosis and the changing age-composition and size of the population, the evidence leaves little doubt that a true increase in lung cancer has taken place.

Deaths from arteriosclerotic, coronary, and degenerative heart disease rose from 273,000 in 1940, to 396,000 in 1950, and to 578,000 in 1962.

Reported deaths from chronic bronchitis and emphysema rose from 2,300 in 1945 to 15,000 in 1962.

The changing patterns and extent of tobacco use are a pertinent aspect of the tobacco-health problem.

TABLE 1.—*Deaths from selected disease categories, United States, 1962*

Cause of death*	Total	Males	Females
Degenerative and arteriosclerotic heart disease, including coronary disease (420, 422)	577,918	348,604	229,314
Hypertensive heart disease (440-3)	62,176	26,654	35,522
Cancer of lung (162-3)	41,376	35,312	6,064
Cirrhosis of liver (581)	21,824	14,329	7,495
Bronchitis and emphysema (502, 527.1)	15,104	12,937	2,167
Stomach and duodenal ulcers (540-1)	12,228	8,836	3,392
Cancer of bladder (181)	8,081	5,575	2,506
Cancer of oral cavity (140-8)	6,481	4,920	1,561
Cancer of esophagus (150)	5,088	3,973	1,115
Cancer of larynx (161)	2,417	2,172	245
All above causes	752,693	463,312	289,391
All other causes	1,004,027	531,477	472,550
All causes	1,756,720	994,789	761,031

*International Statistical Classification numbers in parentheses.

Nearly 70 million people in the United States consume tobacco regularly. Cigarette consumption in the United States has increased markedly since the turn of the Century, when per capita consumption was less than 50 cigarettes a year. Since 1910, when cigarette consumption per person (15 years and older) was 138, it rose to 1,365 in 1930, to 1,828 in 1940, to 3,322 in 1950, and to a peak of 3,986 in 1961. The 1955 Current Population Survey showed that 68 percent of the male population and 32.4 percent of the female population 18 years of age and over were regular smokers of cigarettes.

In contrast with this sharp increase in cigarette smoking, per capita use of tobacco in other forms has gone down. Per capita consumption of cigars declined from 117 in 1920 to 55 in 1962. Consumption of pipe tobacco, which reached a peak of 2½ lbs. per person in 1910, fell to a little more than half a pound per person in 1962. Use of chewing tobacco has declined from about four pounds per person in 1900 to half a pound in 1962.

The background for the Committee's study thus included much general information and findings from previous investigations which associated the increase in cigarette smoking with increased deaths in a number of major disease categories. It was in this setting that the Committee began its work to assess the nature and magnitude of the health hazard attributable to smoking.

KINDS OF EVIDENCE

In order to judge whether smoking and other tobacco uses are injurious to health or related to specific diseases, the Committee evaluated three main kinds of scientific evidence:

1. *Animal experiments.*—In numerous studies, animals have been exposed to tobacco smoke and tars, and to the various chemical compounds they contain. Seven of these compounds (polycyclic aromatic compounds) have been established as cancer-producing (carginogenic). Other substances in tobacco and smoke, though not carcinogenic themselves, promote cancer production or lower the threshold to a known carcinogen. Several toxic or irritant gases contained in tobacco smoke produce experimentally the kinds of non-cancerous damage seen in the tissues and cells of heavy smokers. This includes

suppression of ciliary action that normally cleanses the trachea and bronchi, damage to the lung air sacs, and to mucous glands and goblet cells which produce mucus.

2. *Clinical and autopsy studies.*—Observations of thousands of patients and autopsy studies of smokers and non-smokers show that many kinds of damage to body functions and to organs, cells, and tissues occur more frequently and severely in smokers. Three kinds of cellular changes—loss of ciliated cells, thickening (more than two layers of basal cells), and presence of atypical cells—are much more common in the lining layer (epithelium) of the trachea and bronchi of cigarette smokers than of non-smokers. Some of the advanced lesions seen in the bronchi of cigarette smokers are probably premalignant. Cellular changes regularly found at autopsy in patients with chronic bronchitis are more often present in the bronchi of smokers than non-smokers. Pathological changes in the air sacs and other functional tissue of the lung (parenchyma) have a remarkably close association with past history of cigarette smoking.

3. *Population studies.*—Another kind of evidence regarding an association between smoking and disease comes from epidemiological studies.

In retrospective studies, the smoking histories of persons with a specified disease (for example, lung cancer) are compared with those of appropriate control groups without the disease. For lung cancer alone, 29 such retrospective studies have been made in recent years. Despite many variations in design and method, all but one (which dealt with females) showed that proportionately more cigarette smokers are found among the lung cancer patients than in the control populations without lung cancer.

Extensive retrospective studies of the prevalence of specific symptoms and signs—chronic cough, sputum production, breathlessness, chest illness, and decreased lung function—consistently show that these occur more often in cigarette smokers than in non-smokers. Some of these signs and symptoms are the clinical expressions of chronic bronchitis, and some are associated more with emphysema; in general, they increase with amount of smoking and decrease after cessation of smoking.

Another type of epidemiological evidence on the relation of smoking and mortality comes from seven prospective studies which have been conducted since 1951. In these studies, large numbers of men answered questions about their smoking or non-smoking habits. Death certificates have been obtained for those who died since entering the studies, permitting total death rates and death rates by cause to be computed for smokers of various types as well as for non-smokers. The prospective studies thus add several important dimensions to information on the smoking-health problem. Their data permit direct comparisons of the death rates of smokers and non-smokers, both overall and for individual causes of death, and indicate the strength of the association between smoking and specific diseases.

Each of these three lines of evidence was evaluated and then considered together in drawing conclusions. The Committee was aware that the mere establishment of a statistical association between the use of tobacco and a disease is not enough. The causal significance of the use of tobacco in relation to the disease is the crucial question. For such judgments all three

lines of evidence are essential, as discussed in more detail on pages 26–27 of this Chapter, and in Chapter 3.

The experimental, clinical, and pathological evidence, as well as data from population studies, is highlighted in Section B of this Chapter, which in turn refers the reader to specific places in Part II of the Report where this evidence is presented in detail.

In the paragraphs which follow, the Committee has chosen to summarize the results of the seven prospective population studies which, as noted above, constitute only one type of evidence. They illustrate the nature and potential magnitude of the smoking-health problem, and bring out a number of factors which are involved.

Evidence From the Combined Results of Prospective Studies

The Committee examined the seven prospective studies separately as well as their combined results. Considerable weight was attached to the consistency of findings among the several studies. However, to simplify presentation, only the combined results are highlighted here.

Of the 1,123,000 men who entered the seven prospective studies and who provided usable histories of smoking habits (and other characteristics such as age), 37,391 men died during the subsequent months or years of the studies. No analyses of data for females from prospective studies are presently available.

To permit ready comparison of the mortality experience of smokers and non-smokers, two concepts are widely used in the studies—excess deaths of smokers compared with non-smokers, and mortality ratio. After adjustments for differences in age and the number of cigarette smokers and non-smokers, an expected number of deaths of smokers is derived on the basis of deaths among non-smokers. Excess deaths are thus the number of actual (observed) deaths among smokers in excess of the number expected. The mortality ratio, for which the method of computation is described in Chapter 8, measures the relative death rates of smokers and non-smokers. If the age-adjusted death rates are the same, the mortality ratio will be 1.0; if the death rates of smokers are double those of non-smokers, the mortality ratio will be 2.0. (Expressed as a percentage, this example would be equivalent to a 100 percent increase.).

Table 2 presents the accumulated and combined data on 14 disease categories for which the mortality ratio of cigarette smokers to non-smokers was 1.5 or greater.

The mortality ratio for male cigarette smokers compared with non-smokers, for all causes of death taken together, is 1.68, representing a total death rate nearly 70 percent higher than for non-smokers. (This ratio includes death rates for diseases not listed in the table as well as for the 14 disease categories shown.)

In the combined results from the seven studies, the mortality ratio of cigarette smokers over non-smokers was particularly high for a number of diseases: cancer of the lung (10.8), bronchitis and emphysema (6.1), can-

TABLE 2.[1]—*Expected and observed deaths for smokers of cigarettes only and mortality ratios in seven prospective studies*

Underlying cause of death	Expected deaths	Observed deaths	Mortality ratio
Cancer of lung (162-3) [2]	170.3	1,833	10.8
Bronchitis and emphysema (502, 521.1)	89.5	546	6.1
Cancer of larynx (161)	14.0	75	5.4
Oral cancer (140-8)	37.0	152	4.1
Cancer of esophagus (150)	33.7	113	3.4
Stomach and duodenal ulcers (540, 541)	105.1	294	2.8
Other circulatory diseases (451-68)	254.0	649	2.6
Cirrhosis of liver (581)	169.2	379	2.2
Cancer of bladder (181)	111.6	216	1.9
Coronary artery disease (420)	6,430.7	11,177	1.7
Other heart diseases (421-2, 430-4)	526.0	868	1.7
Hypertensive heart (440-3)	400.2	631	1.5
General arteriosclerosis (450)	210.7	310	1.5
Cancer of kidney (180)	79.0	120	1.5
All causes [3]	15,653.0	23,223	1.68

[1] Abridged from Table 29, Chapter 8, Mortality.
[2] International Statistical Classification numbers in parentheses.
[3] Includes all other causes of death as well as those listed above.

cer of the larynx (5.4), oral cancer (4.1), cancer of the esophagus (3.4), peptic ulcer (2.8), and the group of other circulatory diseases (2.6). For coronary artery disease the mortality ratio was 1.7.

Expressed in percentage-form, this is equivalent to a statement that for coronary artery disease, the leading cause of death in this country, the death rate is 70 percent higher for cigarette smokers. For chronic bronchitis and emphysema, which are among the leading causes of severe disability, the death rate for cigarette smokers is 500 percent higher than for non-smokers. For lung cancer, the most frequent site of cancer in men, the death rate is nearly 1,000 percent higher.

Other Findings of the Prospective Studies

In general, the greater the number of cigarettes smoked daily, the higher the death rate. For men who smoke fewer than 10 cigarettes a day, according to the seven prospective studies, the death rate from all causes is about 40 percent higher than for non-smokers. For those who smoke from 10 to 19 cigarettes a day, it is about 70 percent higher than for non-smokers; for those who smoke 20 to 39 a day, 90 percent higher; and for those who smoke 40 or more, it is 120 percent higher.

Cigarette smokers who stopped smoking before enrolling in the seven studies have a death rate about 40 percent higher than non-smokers, as against 70 percent higher for current cigarette smokers. Men who began smoking before age 20 have a substantially higher death rate than those who began after age 25. Compared with non-smokers, the mortality risk of cigarette smokers, after adjustments for differences in age, increases with duration of smoking (number of years), and is higher in those who stopped after age 55 than for those who stopped at an earlier age.

In two studies which recorded the degree of inhalation, the mortality ratio for a given amount of smoking was greater for inhalers than for non-inhalers.

The ratio of the death rates of smokers to that of non-smokers is highest

at the earlier ages (40–50) represented in these studies, and declines with increasing age.

Possible relationships of death rates and other forms of tobacco use were also investigated in the seven studies. The death rates for men smoking less than 5 cigars a day are about the same as for non-smokers. For men smoking more than 5 cigars daily, death rates are slightly higher. There is some indication that these higher death rates occur primarily in men who have been smoking more than 30 years and who inhale the smoke to some degree. The death rates for pipe smokers are little if at all higher than for non-smokers, even for men who smoke 10 or more pipefuls a day and for men who have smoked pipes more than 30 years.

Excess Mortality

Several of the reports previously published on the prospective studies included a table showing the distribution of the excess number of deaths of cigarette smokers among the principal causes of death. The hazard must be measured not only by the mortality ratio of deaths in smokers and non-smokers, but also by the importance of a particular disease as a cause of death.

In all seven studies, coronary artery disease is the chief contributor to the excess number of deaths of cigarette smokers over non-smokers, with lung cancer uniformly in second place. For all seven studies combined, coronary artery disease (with a mortality ratio of 1.7) accounts for 45 percent of the excess deaths among cigarette smokers, whereas lung cancer (with a ratio of 10.8) accounts for 16 percent.

Some of the other categories of diseases that contribute to the higher death rates for cigarette smokers over non-smokers are diseases of the heart and blood vessels, other than coronary artery disease, 14 percent; cancer sites other than lung, 8 percent; and chronic bronchitis and emphysema, 4 percent.

Since these diseases as a group are responsible for more than 85 percent of the higher death rate among cigarette smokers, they are of particular interest to public health authorities and the medical profession.

Associations and Causality

The array of information from the prospective and retrospective studies of smokers and non-smokers clearly establishes an association between cigarette smoking and substantially higher death rates. The mortality ratios in Table 2 provide an approximate index of the relative strength of this association, for all causes of death and for 14 disease categories.

In this inquiry the epidemiologic method was used extensively in the assessment of causal factors in the relationship of smoking to health among human beings upon whom direct experimentation could not be imposed. Clinical, pathological, and experimental evidence was thoroughly considered and often served to suggest an hypothesis or confirm or contradict other findings. When coupled with the other data, results from the epidemiologic

studies can provide the basis upon which judgments of causality may be made.

It is recognized that no simple cause-and-effect relationship is likely to exist between a complex product like tobacco smoke and a specific disease in the variable human organism. It is also recognized that often the coexistence of several factors is required for the occurrence of a disease, and that one of the factors may play a determinant role; that is, without it, the other factors (such as genetic susceptibility) seldom lead to the occurrence of the disease.

The Effects of Smoking: Principal Findings

Cigarette smoking is associated with a 70 percent increase in the age-specific death rates of males. The total number of excess deaths causally related to cigarette smoking in the U.S. population cannot be accurately estimated. In view of the continuing and mounting evidence from many sources, it is the judgment of the Committee that cigarette smoking contributes substantially to mortality from certain specific diseases and to the overall death rate.

Lung Cancer

Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction.

The risk of developing lung cancer increases with duration of smoking and the number of cigarettes smoked per day, and is diminished by discontinuing smoking. In comparison with non-smokers, average male smokers of cigarettes have approximately a 9- to 10-fold risk of developing lung cancer and heavy smokers at least a 20-fold risk.

The risk of developing cancer of the lung for the combined group of pipe smokers, cigar smokers, and pipe and cigar smokers is greater than for non-smokers, but much less than for cigarette smokers.

Cigarette smoking is much more important than occupational exposures in the causation of lung cancer in the general population.

Chronic Bronchitis and Emphysema

Cigarette smoking is the most important of the causes of chronic bronchitis in the United States, and increases the risk of dying from chronic bronchitis and emphysema. A relationship exists between cigarette smoking and emphysema but it has not been established that the relationship is causal. Studies demonstrate that fatalities from this disease are infrequent among non-smokers.

For the bulk of the population of the United States, the relative importance of cigarette smoking as a cause of chronic broncho-pulmonary disease is much greater than atmospheric pollution or occupational exposures.

Cardiovascular Diseases

It is established that male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males. Although the causative role of cigarette smoking in deaths from coronary disease is not proven, the Committee considers it more prudent from the public health viewpoint to assume that the established association has causative meaning than to suspend judgment until no uncertainty remains.

Although a causal relationship has not been established, higher mortality of cigarette smokers is associated with many other cardiovascular diseases, including miscellaneous circulatory diseases, other heart diseases, hypertensive heart disease, and general arteriosclerosis.

Other Cancer Sites

Pipe smoking appears to be causally related to lip cancer. Cigarette smoking is a significant factor in the causation of cancer of the larynx. The evidence supports the belief that an association exists between tobacco use and cancer of the esophagus, and between cigarette smoking and cancer of the urinary bladder in men, but the data are not adequate to decide whether these relationships are causal. Data on an association between smoking and cancer of the stomach are contradictory and incomplete.

The Tobacco Habit and Nicotine

The habitual use of tobacco is related primarily to psychological and social drives, reinforced and perpetuated by the pharmacological actions of nicotine.

Social stimulation appears to play a major role in a young person's early and first experiments with smoking. No scientific evidence supports the popular hypothesis that smoking among adolescents is an expression of rebellion against authority. Individual stress appears to be associated more with fluctuations in the amount of smoking than with the prevalence of smoking. The overwhelming evidence indicates that smoking—its beginning, habituation, and occasional discontinuation—is to a very large extent psychologically and socially determined.

Nicotine is rapidly changed in the body to relatively inactive substances with low toxicity. The chronic toxicity of small doses of nicotine is low in experimental animals. These two facts, when taken in conjunction with the low mortality ratios of pipe and cigar smokers, indicate that the chronic toxicity of nicotine in quantities absorbed from smoking and other methods of tobacco use is very low and probably does not represent an important health hazard.

The significant beneficial effects of smoking occur primarily in the area of mental health, and the habit originates in a search for contentment. Since no means of measuring the quantity of these benefits is apparent, the Committee finds no basis for a judgment which would weigh benefits against hazards of smoking as it may apply to the general population.

The Committee's Judgment in Brief

On the basis of prolonged study and evaluation of many lines of converging evidence, the Committee makes the following judgment:

Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action.

B. COMMENTS AND DETAILED CONCLUSIONS

(A Guide to Part II of the Report)

All conclusions formally adopted by the Committee are presented at the end of this section in bold-faced type for convenience of reference. In the interest of conciseness, the documentation and most of the discussion are omitted from this condensation. Together with the tables of contents which appear at the beginning of each chapter in Part II, it is intended as a guide to the Report.

Chemistry and Carcinogenicity of Tobacco and Tobacco Smoke

Condensates of tobacco smoke are carcinogenic when tested by application to the skin of mice and rabbits and by subcutaneous injection in rats (Chapter 9, pp. 143–145). Bronchogenic carcinoma has not been produced by the application of tobacco extracts, smoke, or condensates to the lung or the tracheobronchial tree of experimental animals with the possible exception of dogs (Chapter 9, p. 165).

Bronchogenic carcinoma has been produced in laboratory animals by the administration of polycyclic aromatic hydrocarbons, certain metals, radioactive substances, and viruses. The histopathologic characteristics of the tumors produced are similar to those observed in man and are predominantly of the squamous variety (Chapter 9, pp. 166–167).

Seven polycyclic hydrocarbon compounds isolated from cigarette smoke have been established to be carcinogenic in laboratory animals. The results of a number of assays for carcinogenicity of tobacco smoke tars present a puzzling anomaly: the total tar from cigarettes has many times the carcinogenic potency of benzo(a)pyrene present in the tar. The other carcinogens known to be present in tobacco smoke are, with the exception of dibenzo(a,i)pyrene, much less potent than benzo(a)pyrene and they are present in smaller amounts. Apparently, therefore, the whole is greater than the sum of the known parts. This discrepancy may possibly be due to the presence of cocarcinogens in tobacco smoke, and/or damage to mucus production and ciliary transport mechanism (Chapter 6, p. 61, Chapter 9, p. 144 and Chapter 10, pp. 267–269).

There is abundant evidence that cancer of the skin can be induced in man by industrial exposure to soots, coal tar, pitch, and mineral oils. All of these

contain various polycyclic aromatic hydrocarbons proven to be carcinogenic in many species of animals. Some of these hydrocarbons are also present in tobacco smoke. It is reasonable to assume that these can be carcinogenic for man also (Chapter 9, pp. 146–148).

Genetic factors play a significant role in the development of pulmonary adenomas in mice. It is possible that genetic factors can influence the smoking habit and the response in man to carcinogens in smoke. However, there is no evidence that they have played an appreciable role in the great increase of lung cancer in man since the beginning of this century (Chapter 9, p. 190).

Components of the gas phase of cigarette smoke have been shown to produce various undesirable effects on test animals or organs. One of these effects is suppression of ciliary transport activity, an important cleansing function in the trachea and bronchi (Chapter 6, p. 61 and Chapter 10, pp. 267–270).

Characterization of the Tobacco Habit

The habitual use of tobacco is related primarily to psychological and social drives, reinforced and perpetuated by the pharmacological actions of nicotine on the central nervous system. Nicotine-free tobacco or other plant materials do not satisfy the needs of those who acquire the tobacco habit (Chapter 13, p. 354).

The tobacco habit should be characterized as an habituation rather than an addiction. Discontinuation of smoking, although possessing the difficulties attendant upon extinction of any conditioned reflex, is accomplished best by reinforcing factors which interrupt the psychogenic drives. Nicotine substitutes or supplementary medications have not been proven to be of major benefit in breaking the habit (Chapter 13, p. 354).

Pathology and Morphology

Several types of epithelial changes are much more common in the trachea and bronchi of cigarette smokers, with or without lung cancer, than of nonsmokers and of patients without lung cancer. These epithelial changes are (a) loss of cilia, (b) basal cell hyperplasia, and (c) appearance of atypical cells with irregular hyperchromatic nuclei. The degree of each of the epithelial changes in general increases with the number of cigarettes smoked. Extensive atypical changes have been seen most frequently in men who smoked two or more packs of cigarettes a day.

Women cigarette smokers, in general, have the same epithelial changes as men smokers. However, at given levels of cigarette use, women appear to show fewer atypical cells than do men. Older men smokers have more atypical cells than younger men smokers. Men who smoke either pipes or cigars have more epithelial changes than non-smokers, but have fewer changes than cigarette smokers consuming approximately the same amount of tobacco. Male ex-cigarette smokers have less hyperplasia and fewer atypical cells than current cigarette smokers.

It may be concluded, on the basis of human and experimental evidence, that some of the advanced epithelial hyperplastic lesions with many atypical

cells, as seen in the bronchi of cigarette smokers, are probably premalignant (Chapter 9, pp. 167–173).

Typing of Tumors.—Squamous and oval-cell carcinomas (Group I of Kreyberg's classification) comprise the predominant types associated with the increase of lung cancer in the male population. In several studies, adenocarcinomas (Group II) have also shown a definite increase, although to a much lesser degree. The histological typing of lung cancer is reliable, but the use of the ratio of histological types as an index of the magnitude of increase in lung cancer is of limited value (Chapter 9, pp. 173–175).

Functional and Pathological Changes.—Cigarette smoke produces significant funtional alterations in the trachea, bronchus, and lung. Like several other agents, cigarette smoke can reduce or abolish ciliary motility in experimental animals. Postmortem examination of bronchi from smokers shows a decrease in the number of ciliated cells, shortening of the remaining cilia, and changes in goblet cells and mucous glands. The implication of these morphological observations is that functional impairment would result.

In animal experiments, cigarette smoke appears to affect the physical characteristics of the lung-lining layer and to impair alveolar (air sac) stability. Alveolar phagocytes ingest tobacco smoke components and assist in their removal from the lung. This phagocytic clearance mechanism breaks down under the stress of protracted high-level exposure to cigarette smoke, and smoke components accumulate in the lungs of experimental animals (Chapter 10, pp. 269–270).

The chronic effects of cigarette smoking upon pulmonary function are manifested mainly by a reduction in ventilatory function as measured by the forced expiratory volume (Chapter 10, pp. 289–292).

Histopathological alterations occur as a result of tobacco smoke exposure in the tracheobronchial tree and in the lung parenchyma of man. Changes regularly found in chronic bronchitis—increase in the number of goblet cells, and hypertrophy and hyperplasia of bronchial mucous glands—are more often present in the bronchi of smokers than non-smokers. Cigarette smoke produces significant functional alterations in the upper and lower airways to the lungs. Such alterations could be expected to interfere with the cleansing mechanisms of the lung.

Pathological changes in pulmonary parenchyma, such as rupture of alveolar septa (partitions of the air sacs) and fibrosis, have a remarkably close association with past history of cigarette smoking. These latter changes cannot be related with certainty to emphysema or other recognized diseases at the present time (Chapter 10, pp. 270–275).

Mortality

The death rate for smokers of cigarettes only, who were smoking at the time of entry into the particular prospective study, is about 70 percent higher than that for non-smokers. The death rates increase with the amount smoked. For groups of men smoking less than 10, 10–19, 20–39, and 40 cigarettes and over per day, respectively, the death rates are about 40 percent, 70 per-

cent, 90 percent, and 120 percent higher than for non-smokers. The ratio of the death rates of smokers to non-smokers is highest at the earlier ages (40–50) represented in these studies, and declines with increasing age. The same effect appears to hold for the ratio of the death rate of heavy smokers to that of light smokers. In the studies that provided this information, the mortality ratio of cigarette smokers to non-smokers was substantially higher for men who started to smoke under age 20 than for men who started after age 25. The mortality ratio was increased as the number of years of smoking increased. In two studies which recorded the degree of inhalation, the mortality ratio for a given amount of smoking was greater for inhalers than for non-inhalers. Cigarette smokers who had stopped smoking prior to enrollment in the study had mortality ratios about 1.4 as against 1.7 for current cigarette smokers. The mortality ratio of ex-cigarette smokers increased with the number of years of smoking and was higher for those who stopped after age 55 than for those who stopped at an earlier age (Chapter 8, p. 93).

The biases from non-response and from errors of measurement that are difficult to avoid in mass studies may have resulted in some over-estimation of the true mortality ratios for the complete populations. In our judgment, however, such biases can account for only a part of the elevation in mortality ratios found for cigarette smokers (Chapter 8, p. 96).

Death rates of cigar smokers are about the same as those of non-smokers for men smoking less than five cigars daily. For men smoking five or more cigars daily, death rates were slightly higher (9 percent to 27 percent) than for non-smokers in the four studies that gave this information. There is some indication that this higher death rate occurs primarily in men who have been smoking for more than 30 years and in men who stated that they inhaled the smoke to some degree. Death rates for current pipe smokers were little if at all higher than for non-smokers, even with men smoking 10 or more pipefuls per day and with men who had smoked pipes for more than 30 years. Ex-cigar and ex-pipe smokers, on the other hand, showed higher death rates than both non-smokers and current pipe or cigar smokers in four out of five studies (Chapter 8, p. 94). The explanation is not clear but may be that a substantial number of such smokers stopped because of illness.

Mortality by Cause of Death.—In the combined results from the seven prospective studies, the mortality ratio of cigarette smokers was particularly high for a number of diseases. There is a further group of diseases, including some of the most important chronic diseases, for which the mortality ratio for cigarette smokers lay between 1.2 and 2.0. The explanation of the moderate elevations in mortality ratios in this large group of causes is not clear. Part may be due to the sources of bias previously mentioned or to some constitutional and genetic difference between cigarette smokers and non-smokers. There is also the possibility that cigarette smoking has some general debilitating effect, although no medical evidence that clearly supports this hypothesis can be cited (Chapter 8, p. 105).

In all seven studies, coronary artery disease is the chief contributor to the excess number of deaths of cigarette smokers over non-smokers, with lung cancer uniformly in second place (Chapter 8, p. 108).

For cigar and pipe smokers combined, there was a suggestion of high mortality ratios for cancers of the mouth, esophagus, larynx and lung, and for stomach and duodenal ulcers. These ratios are, however, based on small numbers of deaths (Chapter 8, p. 107).

Cancer by Site

Lung Cancer

Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction.

The risk of developing lung cancer increases with duration of smoking and the number of cigarettes smoked per day, and is diminished by discontinuing smoking.

The risk of developing cancer of the lung for the combined group of pipe smokers, cigar smokers, and pipe and cigar smokers, is greater than for non-smokers, but much less than for cigarette smokers. The data are insufficient to warrant a conclusion for each group individually (Chapter 9, p. 196).

Oral Cancer

The causal relationship of the smoking of pipes to the development of cancer of the lip appears to be established.

Although there are suggestions of relationships between cancer of other specific sites of the oral cavity and the several forms of tobacco use, their causal implications cannot at present be stated (Chapter 9, pp. 204–205).

Cancer of the Larynx

Evaluation of the evidence leads to the judgment that cigarette smoking is a significant factor in the causation of laryngeal cancer in the male (Chapter 9, p. 212).

Cancer of the Esophagus

The evidence on the tobacco-esophageal cancer relationship supports the belief that an association exists. However, the data are not adequate to decide whether the relationship is causal (Chapter 9, p. 218).

Cancer of the Urinary Bladder

Available data suggest an association between cigarette smoking and urinary bladder cancer in the male but are not sufficient to support a judgment on the causal significance of this association (Chapter 9, p. 225).

Stomach Cancer

No relationship has been established between tobacco use and stomach cancer (Chapter 9, p. 229).

Non-Neoplastic Respiratory Diseases, Particularly Chronic Bronchitis and Pulmonary Emphysema

Cigarette smoking is the most important of the causes of chronic bronchitis in the United States, and increases the risk of dying from chronic bronchitis.

A relationship exists between pulmonary emphysema and cigarette smoking but it has not been established that the relationship is causal. The smoking of cigarettes is associated with an increased risk of dying from pulmonary emphysema.

For the bulk of the population of the United States, the importance of cigarette smoking as a cause of chronic bronchopulmonary disease is much greater than that of atmospheric pollution or occupational exposures.

Cough, sputum production, or the two combined are consistently more frequent among cigarette smokers than among non-smokers.

Cigarette smoking is associated with a reduction in ventilatory function. Among males, cigarette smokers have a greater prevalence of breathlessness than non-smokers.

Cigarette smoking does not appear to cause asthma.

Although death certification shows that cigarette smokers have a moderately increased risk of death from influenza and pneumonia, an association of cigarette smoking and infectious diseases is not otherwise substantiated (Chapter 10, p. 302).

Cardiovascular Disease

Smoking and nicotine administration cause acute cardiovascular effects similar to those induced by stimulation of the autonomic nervous system, but these effects do not account well for the observed association between cigarette smoking and coronary disease. It is established that male cigarette smokers have a higher death rate from coronary disease than non-smoking males. The association of smoking with other cardiovascular disorders is less well established. If cigarette smoking actually caused the higher death rate from coronary disease, it would on this account be responsible for many deaths of middle-aged and elderly males in the United States. Other factors such as high blood pressure, high serum cholesterol, and excessive obesity are also known to be associated with an unusually high death rate from coronary disease. The causative role of these factors in coronary disease, though not proven, is suspected strongly enough to be a major reason for taking countermeasures against them. It is also more prudent to assume that the established association between cigarette smoking and coro-

nary disease has causative meaning than to suspend judgment until no uncertainty remains (Chapter 11, p. 327).

Male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males, but it is not clear that the association has causal significance.

Other Conditions

Peptic Ulcer

Epidemiological studies indicate an association between cigarette smoking and peptic ulcer which is greater for gastric than for duodenal ulcer (Chapter 12, p. 340).

Tobacco Amblyopia

Tobacco amblyopia (dimness of vision unexplained by an organic lesion) has been related to pipe and cigar smoking by clinical impressions. The association has not been substantiated by epidemiological or experimental studies (Chapter 12, p. 342).

Cirrhosis of the Liver

Increased mortality of smokers from cirrhosis of the liver has been shown in the prospective studies. The data are not sufficient to support a direct or causal association (Chapter 12, p. 342).

Maternal Smoking and Infant Birth Weight

Women who smoke cigarettes during pregnancy tend to have babies of lower birth weight.

Information is lacking on the mechanism by which this decrease in birth weight is produced.

It is not known whether this decrease in birth weight has any influence on the biological fitness of the newborn (Chapter 12, p. 343).

Smoking and Accidents

Smoking is associated with accidental deaths from fires in the home.

No conclusive information is available on the effects of smoking on traffic accidents (Chapter 12, p. 345).

Morphological Constitution of Smokers

The available evidence suggests the existence of some morphological differences between smokers and non-smokers, but is too meager to permit a conclusion (Chapter 15, p. 387).

Psycho-Social Aspects of Smoking

A clear cut smoker's personality has not emerged from the results so far published. While smokers differ from non-smokers in a variety of characteristics, none of the studies has shown a single variable which is found solely in one group and is completely absent in another. Nor has any single variable been verified in a sufficiently large proportion of smokers and in sufficiently few non-smokers to consider it an "essential" aspect of smoking.

The overwhelming evidence points to the conclusion that smoking—its beginning, habituation, and occasional discontinuation—is to a large extent psychologically and socially determined. This does not rule out physiological factors, especially in respect to habituation, nor the existence of predisposing constitutional or hereditary factors (Chapter 14, p. 377).

PART II

Evidence of the Relation Between Smoking and Health

List of Tables

Chapter 5

Consumption of Tobacco Products in the United States

Chapter 5

CONSUMPTION OF TOBACCO PRODUCTS IN THE UNITED STATES

The U.S. Department of Agriculture estimates that the total number of persons in the United States, including overseas members of the Armed Forces, who consume tobacco on a regular basis is close to 70 million (1).

Consumption of tobacco products per capita, 15 years and over, has risen from 7.42 pounds in 1900 to 10.85 pounds in 1962. Cigarette consumption increased steadily from 1910, when the per capita consumption was 138 cigarettes, to the 1962 figure of 3,958. Per capita cigar consumption remained steady at slightly over 100 in the first two decades of the century, but started to decrease in 1921. The figure for 1920 is 117, and for 1962 it is 55. Per capita consumption of pipe tobacco remained steady until the mid-1940's. In 1945 the figure was 1.59 pounds, but in 1962 it was just over half a pound (0.56). Consumption of chewing tobacco showed a decline during about the same period, from 1.09 pounds per capita in 1945 to 0.50 in 1962. Consumption of snuff has shown very little change (2) (Table 1).

TABLE 1.—*Consumption of tobacco products per person aged 15 years and over in the United States for selected years, 1900–1962*

Year	All tobacco, pounds	Cigarettes, number	Cigars, number	Pipe tobacco, pounds	Chewing tobacco, pounds	Snuff, pounds
1900	7.42	49	111	1.63	4.10	0.32
1910	8.59	138	113	2.56	3.99	.50
1920	8.64	611	117	1.96	3.08	.50
1930	8.88	1,365	72	1.87	1.90	.65
1940	8.91	1,828	55	2.05	1.08	.35
1950	11.59	3,322	50	.94	.75	.36
1960	10.97	3,888	37	.59	.51	.29
1961	11.15	3,998	36	.59	.51	.27
1962	10.85	3,958	55	.56	.50	.28

Source: Department of Agriculture, Economic Research Service.

Starting in 1950, production of filter tip cigarettes began to rise. Unofficial estimates for 1950 show that only about half of one percent of cigarettes produced were filter tip. In 1952, unofficial estimates show 1.3 percent of cigarettes produced were filter tips. In 1956 the figure had reached 27.6 percent. From 1958 on, official estimates, based on figures reported to the Department of Agriculture by the industry, show a continuous increase from 45.3 percent filter tip cigarettes produced in 1958 to 54.6 percent produced in 1962 (3) (Table 2).

TABLE 2.—*Estimated output of filter-tip cigarettes and percentage of total cigarette production, United States, 1950–1962*

Year	Filter-tip cigarettes (billions)	Percent of total	Year	Filter-tip cigarettes (billions)	Percent of total
1950	2.2	0.6	1957	168.3	38.0
1951	3.0	0.7	1958*	213.0	45.3
1952	5.6	1.3	1959	238.6	48.7
1953	12.4	2.9	1960	258.0	50.9
1954	36.9	9.2	1961	277.1	52.5
1955	77.0	18.7	1962	292.5	54.6
1956	116.9	27.6			

*Data from 1958 through 1962 are official estimates from *Census of Manufacturers*.

Source: U.S. Department of Agriculture, Economic Research Service.

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2. U.S. Department of Agriculture. Economic Research Service. Tobacco products. Consumption per capita, 15 years end over, United States, 1900-52.
3. U.S. Department of Agriculture. Economic Research Service. The tobacco situation. March 1962, March 1963, September 1963.

Chapter 6

Chemical and Physical Characteristics of Tobacco and Tobacco Smoke

716-422 O 64—3

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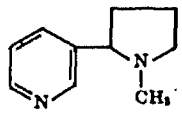
Chapter 6

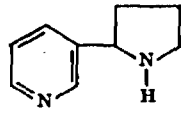
Tobacco is an herb which man has smoked for over 300 years. The plant was given the generic name *Nicotiana* after Jean Nicot, French ambassador to Portugal, who in 1560 publicly extolled the virtue of tobacco as a curative agent. The species *Nicotiana tabacum* is now the chief source of smoking tobacco and is the only species cultivated in the United States.

CHEMISTRY OF TOBACCO

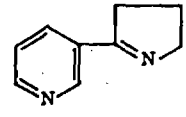
The tobacco leaf contains a complex mixture of chemical components: cellulosic products, starches, proteins, sugars, alkaloids, pectic substances, hydrocarbons, phenols, fatty acids, isoprenoids, sterols, and inorganic minerals. Many of the several hundred components isolated have been found to occur also in other plants. Two groups of components are specific to tobacco and have not as yet been isolated from other natural sources. One includes the alkaloid nicotine and the related companion substances nornicotine, myosmine, and anabasine. These nitrogen-containing substances are all



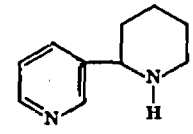
Nicotine



Nornicotine

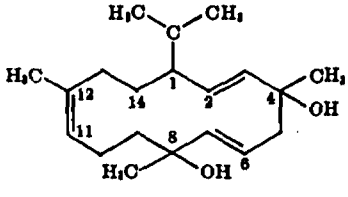


Myosmine

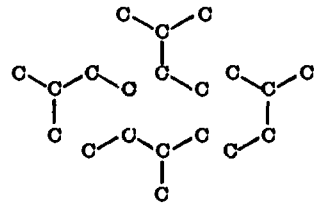


Anabasine

basic and hence extractable with acid. Seven members of a second group of compounds fairly distinctive to tobacco have been isolated and characterized (1962–63) by D. L. Roberts and R. L. Rowland (36). They are described as isoprenoids, since the structures are divisible into units of isoprene, the building principle of rubber, of the red pigment of the tomato, and of the yellow pigment of the carrot, as illustrated in the following formulas:



Isoprenoid tobacco component



4 Isoprene units

Although none of the 7 isoprenoid components of tobacco has been isolated from another source, the hydrocarbon cembrene from a pine exudate has the same 14-membered ring with the same complement of an isopropyl group at C_1 and methyl groups at C_4, C_8, and C_{12} (9).

COMPOSITION OF CIGARETTE SMOKE

Cigarette smoke is an heterogeneous mixture of gases, uncondensed vapors, and liquid particulate matter (32). As it enters the mouth the smoke is a concentrated aerosol with millions or billions of particles per cubic centimeter (25, 30). The median size of the particles is about 0.5 micron (1). For purposes of investigating chemical composition and biological properties, smoke is separated into a particulate phase and a gas phase, and the gas phase is frequently subdivided into materials which condense at liquid-air temperature and those which do not. The large quantities of material required for investigation of the chemical components are prepared on smoking machines (25) in which large numbers of cigarettes are smoked simultaneously in a fashion designed to simulate average smoking habits, and a yellow-brown condensate known as tobacco tar is collected in traps cooled to the temperature of dry ice (−70° C.) or liquid nitrogen (−196° C.). The tar thus contains all of the particulate phase of smoke as well as condensable components of the gas phase. The amount of tar from the smoke of one cigarette is between 3 and 40 mg., the quantity varying according to the burning and condensing conditions, the length of the cigarette, the use of a filter, porosity of paper, content of tobacco, weight and kind of tobacco.

An important factor determining the composition of cigarette smoke is the temperature in the burning zone. While air is being drawn through the cigarette the temperature of the burning zone reaches approximately 884° C. and when the cigarette is burning without air being drawn through it the temperature is approximately 835° C. (42). The smoke generated during puffing, when air is being drawn through the cigarette, is called main-stream smoke; that generated when the cigarette is burning at rest is called side-stream smoke. At the temperatures cited extensive pyrolytic reactions occur. Some of the many constituents of tobacco are stable enough to distil unchanged, but many others suffer extensive reactions involving oxidation, dehydrogenation, cracking, rearrangement, and condensation. The large number and variety of compounds in tobacco smoke tar is reminiscent of the composition of the tar formed on carbonization of coal, which in many cases is conducted at temperatures lower than those of a burning cigarette. It is thus not surprising that some 500 different compounds have been identified in either the particulate phase of cigarette smoke or in the gas phase.

In one study (50) regular cigarettes (70 mm. long, about 1 g. each) without filter tips produced 17–10 mg. of tar per cigarette. In another investigation (43) 174,000 regular size American cigarettes afforded a total of 4 kg. of tar, an average of 23 mg. per cigarette. In still another study (31) 34,000 70-mm. cigarettes were smoked mechanically on a constant puff-volume type machine with which 35-ml. puffs, each of two seconds duration, were taken at one minute intervals from each cigarette. Eight puffs were required to smoke each cigarette to an average butt length of 30 mm. The smoke was condensed in a series of three glass traps cooled in liquid air. The condensate was rinsed out of the traps with ether, water, and hexane. The yield of condensate nonvolatile at 25° C. and 25 mm. of mercury was 20.9 mg. per cigarette.

Procedures for gross separation into basic, acidic, phenolic, and neutral fractions and for further processing of these fractions vary from laboratory to laboratory. The criteria upon which identification is based also vary. The most reliable identifications are based upon an ultraviolet absorption spectrum and/or a fluorescence spectrum in good agreement over the entire range with that of an authentic sample and include one or more of the following: Rf value observed in a paper chromatogram (41); order of elution from alumina; mass spectrometry.

COMPOUNDS OF THE PARTICULATE PHASE OTHER THAN HIGHER POLYCYCLICS

This brief summary is based largely on the comprehensive review by Johnstone and Plimmer of the Medical Research Council at Exeter University, England (24). It should be noted that water constitutes 27 percent of the particulate phase. The major groups of compounds included are shown in Table 1.

Aliphatic and Alicyclic Hydrocarbons

Almost all of the possible hydrocarbons, C_1 through C_4, saturated and unsaturated, straight-chain and branched-chain, have been reported to be present in tobacco smoke. Intermediate, normally liquid paraffins are present. All the C_{26} through C_{33} *n*-alkanes have been identified, as well as the C_{21} and C_{20}-C_{33} isoparaffins.

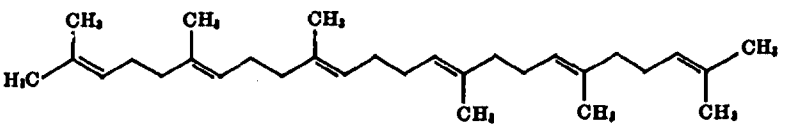
Table 1.—*Major classes of compounds in the particulate phase of cigarette smoke*

Class	Percent in particulate* phase	Number of compounds	Toxic action on lung
Acids	7.7-12.8	25	Some irritant
Glycerol, glycol, alcohols	5.3-8.3	18	Possible irritation
Aldehydes and ketones	8.5	21	Some irritant
Aliphatic hydrocarbons	4.9	64	Some irritant
Aromatic hydrocarbons	0.44	81	Some carcinogenic
Phenols	1.0-3.8	45	Irritant and possibly cocarcinogenic
	60%	254	

*Water 27%.

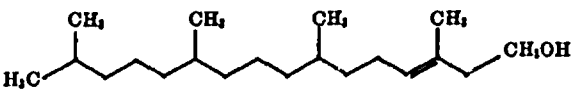
Terpenes and Isoprenoid Hydrocarbons

Isoprene, the basic unit of the terpenes and of higher terpenoids has been identified in cigarette smoke (34) as have its dimers, dipentene and 1,8-*p*-menthadiene. The triterpene squalene, consisting of six isoprene units and shown to be present in smoke (47) is of interest because of the possibility of its being cyclized to polycyclic compounds and because of its ready



Squalene

reaction with air to form hydroperoxides (which would be destroyed during attempted isolation); a hydroperoxide derived from cholesterol has been shown to be carcinogenic (cancer-causing), at least under certain conditions of administration (12). Phytadienes, products of the dehydration of the diterpene alcohol phytol, are also present in smoke and subject to air oxidation to hydroperoxides.



Phytol

Alcohols and Esters

A wide variety of mono- and dihydric alcohols, both aliphatic and aromatic, are present in tobacco smoke. Solanesol, a primary alcohol containing 9 isoprene units, has been found in both tobacco and tobacco smoke; 20 g. of pure material was isolated from 10 lbs. of flue-cured aged tobacco (0.44 percent). Grossman et al (13) found that pyrolysis of solanesol at 500° C. gives isoprene, its dimer dipentene, and other terpenoid products and concluded that the alcohol is the source of terpenoid compounds which are important factors in the flavor of tobacco smoke.

Ethylene glycol and glycerol have been found present in smoke, but it is not clear from the literature whether they are present in smoke from untreated tobacco or arise from addition of these humectant substances to tobacco to improve moistness.

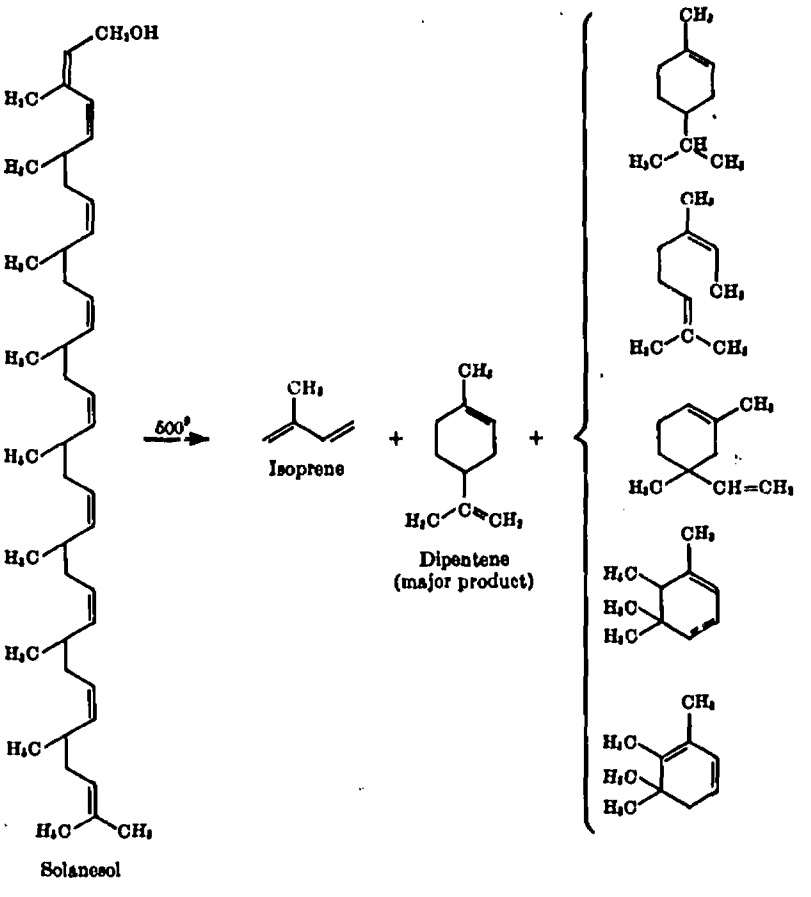
Many common esters, such as the ethyl esters of the C_2, C_3, and C_4 fatty acids, are present in smoke. Higher fatty acids are found both as free acids and as esters.

Sterols

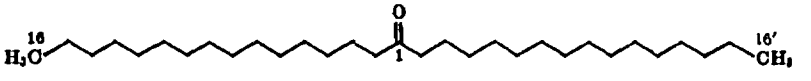
Stigmasterol, β-sitosterol, and γ-sitosterol have been isolated from tobacco smoke. Indeed the sterol fraction is reported (29) to constitute approximately 0.15 percent of whole tar. The sterols are of interest as possible precursors of polycyclic aromatic hydrocarbons and because of the evidence, noted above, that sterol hydroperoxides can be carcinogenic.

Aldehydes and Ketones

Most common aldehydes of low molecular weight (acetaldehyde, propionaldehyde, acetone, methyl ethyl ketone, etc.) have been found present



in tobacco smoke, as have such dicarbonyl compounds as glyoxal and diacetyl. Dipalmityl ketone exemplifies ketones of high molecular weight isolated from tobacco smoke.



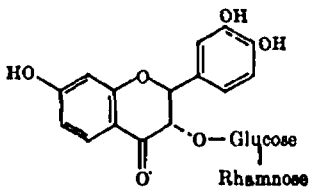
Dipalmityl ketone

Acids

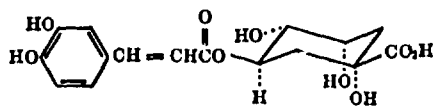
A large number of volatile and nonvolatile acids of low molecular weight are present in tobacco smoke. Fatty acids of chain length C_{13} to C_{18} are reported to constitute 1 percent of the whole tar and the bulk of these acids are present in the free form (46). Unsaturated fatty acids and keto acids (e.g., pyruvic acid) are also present.

Phenols and Polyphenols

Since the phenols and polyphenols present in tobacco leaf play an important role in the curing and smoking quality of tobacco, a great deal of investigative work has been done on the estimation, separation, and identification of complex tobacco phenols such as rutin and chlorogenic acid. The presence of simple phenols in tobacco smoke was established as early as 1871. The phenol content of smoke became of increasing importance with



Rutin

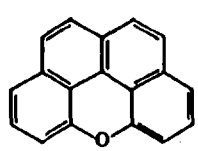


Chlorogenic acid

the demonstration that phenol and substituted phenols can function as cocarcinogens; that is, they promote the appearance of skin tumors in mice following application of a single initiating dose of a known carcinogen (4). Furthermore, the smoke from one cigarette contains as much as 1 mg. of phenols (7). In addition to simple alkylphenols, naphthols, and the polyphenols, resorcinol and hydroquinone are also present.

Alkaloids, Nitrogen Bases, and Heterocyclics

Pyridine, nicotine, nornicotine, and other substituted pyridine bases constitute some 8–15 percent of whole tar; nicotine and nornicotine constitute about 7–8 percent of the total tar. The companion bases are products of the pyrolysis of the alkaloids present in tobacco leaf. Quinoline and three polycyclic heterocyclic compounds have also been identified in smoke (45) and will be discussed later since the three polycyclic compounds are carcinogenic. A pentacyclic compound related to xanthene, namely 1,8,9-perinaphthoxanthene, has been identified in smoke (45).



1,8,9-Perinaphthoxanthene

Amino Acids

Although tobacco leaf contains a number of amino acids, relatively few have been found present in smoke; among these are glutamine and glutamic acid.

Inorganic Components

It is estimated that the main-stream smoke from one cigarette contains about 150 μg. of metallic constituents, which are mainly potassium (90 percent), sodium (5 percent), and traces of aluminum, arsenic, calcium, and copper. Arsenic is reported to be present to the extent of 0.3–1.4 μg. in the smoke of one cigarette. The inorganic compounds are most likely chlorides, but metals themselves may be present.

Apparently beryllium is present in tobacco in trace quantities, but is not volatilized in the smoking process (48). Nickel is present in cigarettes in trace amounts and may occur in main-stream smoke to a small extent, probably as the chloride (31). Spectrographic analysis has shown the presence of chromium in smoke at a level of less than 0.06 μg. per cigarette. This level appears too low to represent a hazard (48).

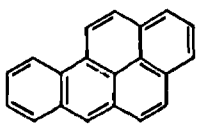
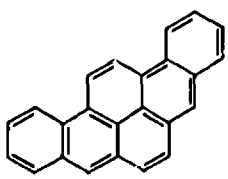
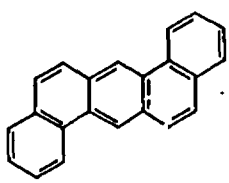
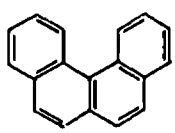
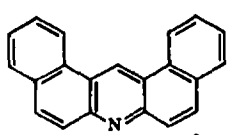
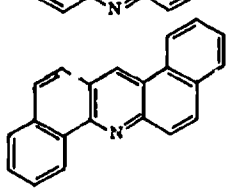
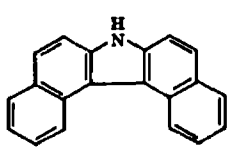
Noncarcinogenic Aromatic Hydrocarbons

The aromatic hydrocarbons present in tobacco smoke have received an enormous amount of attention since some of them are carcinogenic. Noncarcinogenic hydrocarbons of smoke containing one to three rings include benzene, toluene and other alkylbenzenes, acenaphthene, acenaphthylene, fluorene, anthracene, and phenanthrene. Hydrocarbons of established carcinogenicity to mice all contain from four to six condensed rings. However, no less than 27 hydrocarbons containing four or more condensed rings which have been tested for carcinogenicity with negative results have been isolated from tobacco smoke tar. As methods of separation and identification improve, it is almost certain that additional hydrocarbons will be found present in smoke, because almost every conceivable ring system has been demonstrated to be present and the number of possible alkylated polycyclics is very large indeed.

CARCINOGENIC HYDROCARBONS AND HETEROCYCLICS IN TOBACCO SMOKE

In 1925–30 Kennaway et al. in seeking to identify the active substance in high-boiling fractions of coal tar distillates of established carcinogenicity to mice, discovered that dibenzo(a,h)anthracene (for formula, see Table 2) prepared by synthesis evokes skin cancer when applied to the skin of mice (11). The hydrocarbon was recognized as different from the carcinogen of coal tar because its fluorescent spectrum did not match the characteristic three-banded spectrum of the tars. In 1933 Cook and co-workers (11) isolated the coal tar constituent responsible for the characteristic fluorescence and identified it as benzo(a)pyrene. It is one of the most potent of all the carcinogens now known.

TABLE 2.—*Carcinogenic Polycyclic Compounds Isolated From Cigarette Smoke*

Compound	Structure	Carcinogenicity	Amount reported, μg/1000 cigarettes
1. Benzo(a)pyrene		++++	16 (ave. of 10 reports)
2. Dibenzo(a,l)pyrene		++++	0.02-10 (2 reports)
3. Dibenzo(a,h)anthracene		++	4 (1 report)
4. Benzo(c)phenanthrene		+	not stated
5. Dibenz(a,j)acridine		+	2.7 (1 report)
6. Dibenz(a,h)acridine		+	0.1 (1 report)
7. 7H-Dibenzo(c,g)carbazole		+	0.7 (1 report)

Since the discovery of carcinogenic hydrocarbons, a large number of polycyclic hydrocarbons and heterocyclic analogs have been tested for carcinogenicity to mice and to rats in many laboratories, both by application to the skin and by subcutaneous injection. Bioassays in different laboratories, often on independently prepared samples, are remarkably consistent and place a series of hydrocarbons in the same relative order of potency. A compilation (and its supplement) prepared by J. L. Hartwell (16) of the National Cancer Institute lists 2108 compounds of which 481 were reported to cause malignant tumors in animals. All but one of the polycyclic hydrocarbons listed in Table 2 as having been identified in tobacco smoke have already been documented in the Hartwell report and can be assigned a rating as very potent (++++), potent (+++), moderately carcinogenic (++), or weakly carcinogenic (+) (31). Many other such compounds studied are reported in the Hartwell survey and in another by Arthur D. Little, Inc. (31). The rating assigned to dibenzo(a,i) pyrene is based on experiments with over 10,000 inbred mice in which one subcutaneous injection in the groin of 0.5 mg. of hydrocarbon in tricaprylin produced 50 percent sarcomas at the injection site in 14 weeks and 98 percent tumors in 24 weeks (20). Benzo(a)pyrene is one of the two most potent of the seven carcinogens detected in tobacco smoke and it is present in much larger quantity than any of the other carcinogens listed. Two polycyclic hydrocarbons isolated from tobacco smoke but not yet adequately tested for carcinogenicity are: benzo(j)fluoranthene and dibenzo(a,l)pyrene.

Identification of benzo(a)pyrene is reported in 19 separate investigations; the amount given in the table per 1000 cigarettes (70 mm. long, weighing about 1.0 g. each) is the average of 10 values selected on the basis of the quality of criteria used for identification (31). Compounds 1, 2, 3, 4, and benzo(j)fluoranthene were identified in one laboratory over a period of years and are listed together in a review by Van Duuren (44). Isolation of the three heterocyclic carcinogens (5,6,7) is reported by Van Duuren (45).

Because of losses in the process of fractionation and purification, the amount of carcinogens reported in a given investigation may be less than the amount actually present. Wynder and Hoffman (50) investigated this point by adding a known amount of radioactive C^{14}-labelled benzo(a)pyrene to a smoke condensate and applied the usual procedure for isolation of benzo(a)pyrene, which involved, in the last stages, chromatographing twice on silica gel and four times on paper. The activity of the benzo(a)pyrene finally isolated indicated a loss of 35–40 percent of carcinogen during processing. The amount of benzo(a)pyrene given in Table 2 thus should be multiplied by a factor of 1.5 to give the estimated true amount. Probably the amounts of the other carcinogens in smoke are also at least 1.5 times the reported amounts.

Relatively little work has been done on the components of smoke produced with cigars and pipes. Table 3 summarizing a comparative study made in one laboratory (5) indicates that the amount of benzo(a)pyrene, the only carcinogen in the group studied, increases sharply from cigarettes to cigars to pipes.

TABLE 3.—*Polycyclic hydrocarbons isolated from tobacco smoke*

[μg. per 1000 g. of tobacco consumed]

Hydrocarbon	Cigarettes	Cigars	Pipes
Benzo(a)pyrene	9	34	85
Acenaphthylene	50	16	291
Anthracene	109	119	1,100
Pyrene	125	176	755

COCARCINOGENS

Assays of tobacco smoke tars for carcinogenicity are done by applying a dilute solution of tar in an organic solvent with a camel's hair brush to the backs of mice beginning when the animals are about six weeks old. Application is repeated three times a week for a period of a year or more. The results of a number of such assays present a puzzling anomaly: the total tar from cigarettes has about 40 times the carcinogenic potency of the benzo(a)pyrene present in the tar. The other carcinogens known to be present in tobacco smoke are, with the exception of dibenzo(a,i)pyrene, much less potent than benzo(a)pyrene and they are present in smaller amounts. Apparently, therefore, the whole is greater than the sum of the known parts (27, 33, 49).

One possible or partial explanation of the discrepancy is that the tar contains compounds which, although not themselves carcinogenic, can enhance the cancer-producing properties of the carcinogens. Berenblum and Shubik (3), reporting on cocarcinogenesis, described the potentiating effect of croton oil, which itself is noncarcinogenic except in certain strains of mice (4a), on the action of hydrocarbon carcinogens. Phenol is reported to have a similar potentiating effect (4, 50) and, as noted above, cigarette smoke contains considerable phenolic material. Long-chain fatty acid esters (39) and free fatty acids (19) have been shown to function as cocarcinogens, and substances of both types occur abundantly in tobacco smoke. It is possible that the potentiating action of croton oil is due to the presence of fatty acids and their esters. A further observation of possible importance is that some polycyclic hydrocarbons, though very weak or inactive as carcinogens, are capable of initiating malignant growth under the influence of a promoter. Thus benz(a)anthracene, identified in cigarette smoke, is very weak or inactive in initiating malignant growth by itself, but initiates carcinogenesis under the influence of croton oil as promoter (15).

If more were known about the possible cocarcinogenicity of the many inactive components of tobacco smoke, some of the apparent discrepancy between isolation and bioassay data might disappear. It is possible that some of the carcinogenicity of smoke is due to hydroperoxides formed from unsaturated smoke components and destroyed in the isolation procedures. Furthermore both sets of data are far from precise; for example, one estimate of the amount of the highly potent dibenzo(a,i)pyrene per 1000 cigarettes (Table 2) is 0.02μg. and another is 10μg.

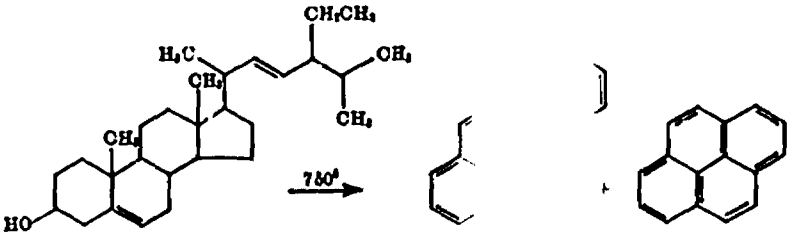
However, it is not necessary to wait for an exact balance of the two sets of data to draw a conclusion from each. The isolation experiments, taken

alone, indicate that cigarette smoke contains a number of identified chemicals which are carcinogenic to mice. The bioassays suggest that cigarette smoke probably contains components which, acting in a manner as yet undescribed, are involved in the induction of tumors in mice.

Assessment of all conceivable synergistic effects presents a gigantic problem for exploration. Tobacco smoke contains considerable amounts of phenols and fatty acids, both of which, as previously mentioned, enhance the activity of known carcinogens. Cellulose acetate filters now in use remove 70-80 percent of acidic constituents of tobacco smoke.

MECHANISM OF THE FORMATION OF CARCINOGENS

Most of the carcinogenic compounds identified in cigarette smoke tar are not present in the native tobacco leaf but are formed by pyrolysis at the high burning temperature of cigarettes. Van Duuren reports formation of benzo(a)pyrene and pyrene on pyrolysis of sterol, a smoke component.



Stigmasterol — Pyrene

Similar pyrolysis of pyridine or of nicotine gives dibenzo(a,j) acridine and dibenzo(a,h)acridine, both of which are carcinogenic (Table 2). Pyrolysis of nontobacco cigarettes made from vegetable fibers and spinach resulted in formation of benzo(a)pyrene (50).

Hurd and co-workers (22) by careful experimentation have elaborated plausible mechanisms for the formation of polycyclic aromatics by pyrolysis of materials of low molecular weight at temperatures in the range 800–900° C. Postulated radical intermediates are:

(a) $CH_2{=}C{=}\dot{C}H \longleftrightarrow \dot{C}H_2{-}C{\equiv}CH$

(b) $\ddot{C}H{-}CH{=}\dot{C}H \longleftrightarrow \dot{C}H{=}CH{-}\ddot{C}H$

(c) $\dot{C}H{=}CH{-}CH{=}\dot{C}H$

These radicals can arise from propylene, toluene, picoline, or pyridine. A variety of polycyclic hydrocarbons can be generated by reaction of these radicals with themselves or with other small radicals present in the heating zone. For example, dimerization of (b) should give benzene.

It thus appears that the pyrolysis of many organic materials can lead to the formation of components carcinogenic to mice. Cigarette paper consists essentially of cellulose. Pyrolysis of cellulose has been shown to produce benzo(a)pyrene. The observation (2) that treatment of tobacco with copper nitrate decreases the benzo(a)pyrene content of the cigarette smoke suggests a possibility for improvement by the use of additives or catalysts. The fact that side-stream smoke contains three times more benzo(a)pyrene than main-stream smoke has been cited (50) as evidence that more efficient oxidation could conceivably lower the content of carcinogenic hydrocarbons.

THE GAS PHASE

The gas phase accounts for 60 percent of total cigarette smoke. Hobbs et al. (34, 35) found that 98.9 mole percent of the gas phase is made up of the following seven components:

Nitrogen	73 mole percent
Oxygen	10
Carbon-dioxide	9.5
Carbon-monoxide	4.2
Hydrogen	1.
Argon	0.6
Methane	0.6
	98.9

The approximately one percent of the gas phase not accounted for by the seven major constituents contains numerous compounds, no less than 43 of which have been identified as present in trace amounts. Some of these are listed in Table 4 (1).

TABLE 4.—*Some gases found in cigarette smoke*

Compound	Concentration	Safe level for industrial exposure*	Toxic action on lung
	(ppm)	(ppm)	
Carbon Monoxide	42,000	100	Unknown
Carbon Dioxide	92,000	.....	None
Methane, ethane, propane, butane, etc.	87,000	500	None
Acetylene, ethylene, propylene, etc.	31,000	5,000	None
Formaldehyde	30	5	Irritant
Acetaldehyde	3,200	200	Irritant
Acrolein	150	0.5	Irritant
Methanol	700	.....	Irritant
Acetone	1,100	200	Irritant
Methyl ethyl ketone	300	200	Irritant
Ammonia	300	150	Irritant
Nitrogen Dioxide	250	5	Irritant
Methyl Nitrite	200	.....	Unknown
Hydrogen Sulfide	60	20	Irritant
Hydrogen Cyanide	1,000	10	Respiratory enzyme poison
Methyl Chloride	1,200	100	Unknown

*The values listed refer to time-weighted average concentrations for a normal work day.

EFFECTS ON CILIARY ACTIVITY*

An important line of investigation was opened up by the report by Hilding (18) that cigarette smoke is capable of inhibiting the transport activity of ciliated cells such as found in the respiratory tract. It has been suggested (10, 17) that failure of ciliary function to provide a constantly moving stream of mucus enables environmental carcinogens to reach the epithelial cells. Kensler and Battista (28) describe development of a method of bioassay for inhibition of ciliary transport activity involving exposure of the trachea of a rabbit to the test material. The smoke from a regular cigarette was found to inhibit transport activity by 50 percent after exposure to two or three puffs. Several commercial filter cigarettes gave essentially the same result. The fact that these filters lower the phenol content by 70 to 80 percent and trap about 40 percent of the particulate phase suggested that neither phenolic nor particulate materials are responsible for the inhibition noted. The next trial was with an absolute filter, that is, one which removes the entire particulate phase and gives nonvisible gas. The observation that such treatment did not significantly alter the inhibitory effect of the puff established that components of the gas phase are responsible for inhibition of ciliary transport activity. Assays of known components of the gas phase showed the following compounds to possess such activity: hydrogen cyanide, formaldehyde, acetaldehyde, acrolein, and ammonia, although no one of these occurs at levels high enough to produce the effect noted for smoke.

Activated carbons differ markedly in their adsorption characteristics. Carbon filters previously employed in cigarettes do not have the specific power to scrub the gas phase. It has been reported that a filter containing special carbon granules removes gaseous constituents which depress ciliary activity (28).

PESTICIDES AND ADDITIVES

Before 1930 practically the only insecticides used in the growing of tobacco were lead arsenate and paris green (the mixed acetate-arsenite salt of copper). Analysis of 6 brands of American cigarettes purchased in 1933 showed a range of 7.5–26.4 parts of As_2O_3 per million, with an average value of 13.9 ppm. (6). Cogbill and Hobbs (8) found that main-stream smoke of cigarettes containing 7.1 μg. of arsenic per cigarette contains 0.031 μg. per puff. This amount would be equivalent to 0.25 μg. of arsenic per cigarette (8 puffs), and hence a smoker consuming 2.5 packs of such cigarettes per day might inhale 12.5 μg. of arsenic per day. By comparison, analysis of the atmosphere of New York City over a 12-year period indicated an average content of 100–400 μg. of arsenic per 10 cubic meters, which is an approximate daily intake per person (38).

Extensive Federal efforts to discourage the use of arsenicals for the control of tobacco hornworms on the growing tobacco crop resulted in a sharp de-

*This topic is discussed more fully in Chapter 10.

cline in the arsenic content of cigarettes after 1950. Thus, the average arsenic content of 17 brands of cigarettes analyzed in 1958 was 6.2 ppm. of As_2O_3 (14).

It seems unlikely that the amount of arsenic derived even from unfiltered cigarettes is sufficient to present a health hazard.

Chemicals recommended by the Department of Agriculture for the control of tobacco insects are: malathion, parathion, Endosulfan, DDT, TDE, endrin, dieldrin, Guthion, aldrin, heptachlor, Diazinon, Dylox, Sevin, and chlordane (42a). Trace amounts of TDE and endrin have been detected in commercial cigarettes and cigarette smoke. Guthion and Sevin residues were detected in main-stream cigarette smoke at levels approximating 0.3 percent and 1 percent of that added to cigarettes prior to smoking. Tobacco treated with Guthion and Sevin at the recommended levels showed no measurable contamination of main-stream cigarette smoke (4b). (For discussion of carcinogenicity of tobacco pesticides, see Chapter 9.)

Cigarette manufacture in the United States includes use of additives such as sugars, humectants, synthetic flavors, licorice, menthol, vanillin, and rum. Glycerol and methylglycerol are looked on with disfavor as humectants because on pyrolysis they yield the irritants acrolein and methylglyoxal. Additives have not been used in the manufacture of domestic British cigarettes since the Customs and Excise Act of 1952, Clause 176, and probably longer, inasmuch as Section 5 of the Tobacco Act of 1842 imposed a widespread prohibition on the use of additives in tobacco manufacture.

SUMMARY

Of the several hundred compounds isolated from the tobacco leaf, two groups are specific to tobacco. One of these groups includes the alkaloid nicotine and related substances. The other includes compounds described as isoprenoids. Cigarette smoke is an heterogeneous mixture of gases, uncondensed vapors, and particulate matter. In investigating chemical composition and biological properties, it is necessary to deal separately with the particulate phase and gas phase of smoke.

Components of the particulate phase other than the higher polycyclics include aliphatic and alicyclic hydrocarbons, terpenes and isoprenoid hydrocarbons, alcohols and esters, sterols, aldehydes and ketones, acids, phenols and polyphenols, alkaloids, nitrogen bases, heterocyclics, amino acids, and inorganic chemicals such as arsenic, potassium, and some metals. Seven polycyclic compounds isolated from cigarette smoke have been established to be carcinogenic. They are shown in Table 2. The over-all carcinogenic potency of tobacco tar is many times the effect which can be attributed to substances isolated from it. The difference may be associated in part with the presence in tobacco smoke of cocarcinogens, several of which have been identified as smoke components.

Components of the gas phase of cigarette smoke have been shown to produce various undesirable effects on test animals or organs, one of which is suppression of ciliary transport activity in trachea and bronchi.

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Chapter 7

Pharmacology and Toxicology of Nicotine

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Chapter 7

GENERAL PHARMACOLOGIC ACTION OF NICOTINE ON NERVE CELLS

The pharmacology and chronic toxicity of nicotine, in dosage comparable to the amounts that man may absorb from smoking or other use of tobacco, are pertinent to an evaluation of health hazard.

The most notable action of nicotine involves a direct effect on sympathetic and parasympathetic ganglion cells (18). This usually occurs as a transient excitation, followed by depression, or even paralysis with effective doses. The ganglia are rendered more sensitive to acetylcholine initially and thus make preganglionic impulses more effective. Paralysis is associated with diminished sensitivity of ganglia to acetylcholine and concomitant reduction in the intensity of postganglionic discharges. Similar effects occur at the neuromuscular junction, resulting in a curariform action in skeletal muscle with adequate doses (16). In the central nervous system, as in ganglia, primary stimulation is succeeded by depression. Furthermore, nicotine like acetylcholine discharges epinephrine from the adrenal glands and other chromaffin tissue (20); it also releases antidiuretic hormone from the posterior pituitary by stimulating the supraopticohypophyseal system (3). Nicotine also augments various reflexes by excitation of chemoreceptors in the carotid body (10).

The pharmacological response of the whole organism at any one time therefore, representing as it does the algebraic sum of stimulant and depressant effects resulting from many direct, reflex, and chemical mediator influences on autonomic nervous transmission and excitability of virtually all organ systems, defies accurate description. The wide variation in smoking habits leads to every conceivable pattern of fluctuating blood levels of nicotine during the day. This suggests strongly that nicotine-sensitive cells may be shifting continuously from excitation to depression. Such activity probably accounts for the unpredictable effects observed in different individuals and in the same individual at different times. Using the classic pharmacological approach, it is therefore virtually impossible to make reliable statements regarding the effect of smoking on the many organ systems. In order to characterize the biological effects of nicotine in man, it thus becomes necessary to place heavy reliance on symptoms and signs derived from clinical and epidemiological studies.

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

The action of nicotine on central nervous system functions has recently been reviewed (20). Very little of the reported work involves human

experimentation, and most of it is with doses much larger than are associated with the act of smoking. It suffices to note here that moderate doses of nicotine elicit marked increases in respiratory, vasomotor, and emetic activity, and still larger doses lead to tremors and convulsions, both in animals and man. The amounts absorbed even in heavy smoking may produce transient hyperpnea through carotid and aortic arch reflexes (5). The increase in blood pressure which is commonly observed is partly central in origin. Nausea and emesis are more pronounced in the novice smoker but may occur even in heavy smokers with excessive use of tobacco. Electroencephalographic (EEG) studies in the intact rabbit (21) indicate that nicotine, in doses of 0.5 to 3.0 milligrams per kilogram, produced an "arousal reaction" involving the hippocampus. In a later stage of the same reaction there appeared a discharge pattern similar to that noted in convulsions. Lesions in the septum abolished the "arousal reaction," chlorpromazine and evipan abolished the discharge pattern. None of the congeners of nicotine, including lobeline, produced similar patterns.

Knapp and Domino (12) found that concentrations of nicotine (10 to 20 μg/kg), a level commonly reached in man by smoking, produced EEG arousal patterns in four species of animals, the rabbit, cat, dog, and monkey, after mesopontine transection. These effects did not appear to be related to fluctuations in blood pressure or to catecholamine or serotonin levels.

In a study of electrical activity (as measured by electroencephalogram) in 25 human subjects before and after smoking one cigarette, Lambiase and Serra (15) noted an 80 percent depression in voltage and an acceleration in frequency of the alpha rhythm which remained unchanged in form during the recordings. These alterations were more consistent in subjects over 35 years of age and were attributed to carbon monoxide and nicotine resulting in cerebral anoxia and/or release of epinephrine. Hauser et al. (9), who studied the EEG changes on cigarette smoking in healthy young adults, obtained highly variable responses usually toward an increase in the dominant alpha frequency of 1 or 2 cycles per second. Some subjects showed similar changes when puffing a glass cigarette stuffed with cotton and others when puffing specially prepared nicotine-free cigarettes. They concluded that the effects noted were more likely to represent a psycho-physiologic response to the act of smoking than to any substances present in cigarette smoking. Bickford (1) arrived at a similar conclusion. Wide gaps of information exist in this area and it is not meaningful to attempt inferences concerning correlations of electrical events in the central nervous system and subjective effects of smoking from the type of evidence currently available.

CARDIOVASCULAR EFFECTS

The cardiovascular effects of nicotine are described in Chapter 11, Cardiovascular Diseases.

GASTROINTESTINAL EFFECTS

Most but not all experimental and clinical evidence supports the popular view that smoking reduces appetite (6, 17 p. 271). This reduction has been attributed both to direct effects on gastric secretions and motility and to reflexes arising from local effects on the taste buds and mucous membranes in the mouth. The unpredictable and temporary elevation of blood sugar is probably too small to contribute significantly (17, p. 326). Nicotine effects on the hypothalamus, comparable to the appetite reduction produced by other stimulants like amphetamine, and psychological mechanisms may play significant roles (23). Hunger contractions are inhibited but gastric movements of digestion do not appear to be influenced significantly by moderate smoking (4).

Nausea, often associated with vomiting, is by far the most common symptom related to the gastrointestinal tract. This effect probably originates centrally in the medullary emetic chemoreceptor trigger zone (14). It is now generally agreed that nicotine stimulates peristalsis but the mechanism is a complex one, probably involving local, central and reflex actions. Schnedorf and Ivy (21) found wide individual variation in gastrointestinal passage time in medical student smokers and non-smokers but gained the impression that smoking tends to augment motility of the colon. These effects are probably related to actions on the parasympathetic ganglia in the bowel. The summative effects of all of these pharmacological actions on the whole intestinal tract do not produce a consistent pattern. Excessive smoking may be associated with diarrhea, constipation, or alternating patterns between the two extremes. The only consistency is that symptoms attributable to nicotine effects on the gastrointestinal tract are very common.

DISTRIBUTION AND FATE

Nicotine is actively and rapidly metabolized by man and other mammals, the metabolites being in large measure excreted in the urine. If any tissue storage occurs, it is in such small quantity as to elude current analytical technics. Nicotine is a rather unstable molecule which in neutral or alkaline conditions undergoes a variety of changes. A review of the current concepts of the known and suggested pathways for the metabolism of nicotine is shown in Figure 1 (18). The main intermediate appears to be (−)-cotenine which yields γ-(3-pyridyl)-γ-methylamino butyric acid. Cotenine has low toxicity and lacks the potent pressor activity of nicotine.

Dogs receiving 150 mg/kg/day orally for 108 days exhibited no weight loss or other objective signs (2). Man has ingested 500 mg orally at 8-hour intervals for 6 days without untoward effects. No evidence has been presented that the other known metabolites of nicotine carry any significant systemic toxicity.

SUMMARY DIAGRAM OF ROUTES FOR THE METABOLISM OF NICOTINE IN MAMMALS

(Some hypothetical intermediates are shown in brackets.)

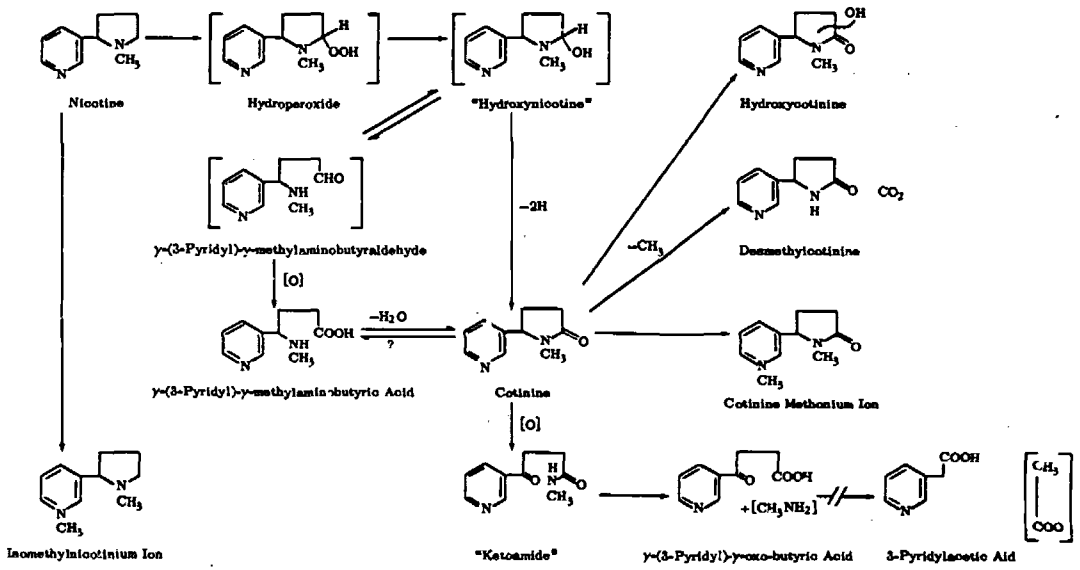

FIGURE 1.

Source: McKennis, Herbert H., Jr. (18)

CHRONIC TOXICITY

Evaluation of the chronic toxicity of tobacco smoke may be considered in several categories: (a) the systemic toxicity of nicotine or its congeners, (b) the systemic toxicity of other constituents of smoke or tobacco, carbon monoxide and other compounds, (c) specific organ toxicity in certain susceptible individuals, such as those with Buerger's disease and allergic responses, (d) local effect of irritants on mucous and pulmonary membranes by tars, phenols, the oxides of nitrogen, and others. The latter three types of potential toxicity are discussed in Chapter 9, Cancer, and Chapter 10, Non-Neoplastic Respiratory Diseases.

It might appear that the least difficult problem in this group of variables would be to assess the chronic toxicity of nicotine since we are dealing with a comparatively simple organic compound of known composition and reaction. Whereas there is a voluminous literature of studies involving chronic exposure to nicotine or tobacco smoke in many animal species (17, pp. 501–504), most of these are poorly designed and controlled and are of little value for extrapolation to man. For example, in the best nicotine experiments involving life span studies, the daily dose of nicotine was near the maximal tolerated dose (just subconvulsive), which is greatly in excess of any human smoking exposure. Even though some authors (11) observed weight loss and degenerative vascular changes in rats under these severe conditions, others (22) noted some weight loss but no histologic change. In life span experiments in rats, with tobacco smoke in amounts approximating human smoking exposure, very little systemic toxicity was noted (8, 13). Even though animal experimentation is inadequate, especially in long-term effects of nicotine on large animal species, existing data permits a tentative conclusion that the chronic systemic toxicity of nicotine is quite low in small to moderate dosage.

The clinical literature is devoid of human data concerning chronic exposure to nicotine alone, and the general statements regarding the chronic toxicity of nicotine for man represent inferences drawn from chronic exposure to tobacco in various forms, including industrial poisoning. Repeated exposure to tobacco in excessive amounts is reported to induce amblyopia, arrhythmias, digestive disturbances, cachexia and a wide variety of other signs and symptoms. But the effects of excessive dose are of little concern here. The question is whether prolonged *exposure to nicotine*, in the quantities absorbed systemically from smoking or other tobacco use, produces toxic effects which result in unpleasant symptoms, dangerous signs, specific degenerative disease, or shortening of the life span. Unfortunately even a tentative answer to this question must be obtained indirectly and by making certain assumptions. Inasmuch as nicotine is systemically absorbed from all routes of administration, smoking, chewing, snuffing, or "snuff dipping,"* it appears logical to assume that if the amounts of nicotine absorbed in the various methods of use are of the same order of magnitude, any toxic effects observed should also be in this order of magnitude. There appears to be general agreement that this is so. Calculations indicate that the nicotine

*A small amount of snuff is placed in the groove between the teeth and the lower lip or beneath the tongue and held there from 30 minutes to several hours.

absorbed (40–60 mg) from 6 cigars uninhaled equals that from 30 cigarettes inhaled (19). Chewing tobacco may yield 8 to 87 mg in 6 to 8 hours (24); in chewing snuff, 20–60 mg of nicotine (7).

The following variables play a role in the amount of nicotine absorbed (17, p. 8):

> To sum up, the rate and amount of absorption of nicotine by the smoker depend to a greater or less extent upon the following factors:
>
> 1. Length of time the smoke remains in contact with the mucous membranes;
> 2. pH of the body fluids with which the smoke comes in contact;
> 3. Degree and depth of inhalation;
> 4. Degree of habituation of the smoker (?);
> 5. Nicotine content of the tobacco smoked;
> 6. Moisture content of the tobacco smoked;
> 7. Form in which tobacco is smoked (cut [cigarettes] or uncut [cigars]) (?);
> 8. Length of butt;
> 9. Use of holder or filter;
> 10. Alkalinity or acidity of the tobacco smoke (?);
> 11. Agglomeration of smoke particles (more important in cigarette-smoking).

There is no acceptable evidence that prolonged exposure to nicotine creates either *dangerous* functional change of an objective nature or degenerative disease. The minor evidences of toxicity, nausea, digestive disturbances and the like, are similar in kind and degree with all forms of use.

The fact that the over-all death rates of pipe and cigar smokers show little if any increase over non-smokers is very difficult to reconcile with a concept of high nicotine toxicity. In view of the mortality ratios of pipe and cigar smokers, it follows logically that the apparent increase in morbidity and mortality among cigarette smokers relates to exposure to substances in smoke other than nicotine. Unfortunately, there are no useful mortality statistics in those who chew, snuff, or "dip" tobacco, and the literature regarding industrial exposure is so confusing that little help is available here. The type of projection made above, however unsatisfactory, is not inconsistent with the animal toxicity data as well as the fact that nicotine undergoes very rapid metabolism to substances of low toxicity. The evidence therefore supports a conclusion that the chronic toxicity of nicotine in amounts ordinarily obtained in common forms of tobacco use is very low indeed.

SUMMARY

The pharmacological effects of nicotine at dosage levels absorbed from smoking (1–2 mg per inhaled cigarette) are comparatively small; the response in any point in time represents the algebraic sum of stimulant and depressant actions from direct, reflex, and chemical mediator influences on the several organ systems. The predominant actions are central stimulation and/or tranquilization which vary with the individual, transient hyperpnea,

peripheral vasoconstriction usually associated with a rise in systolic pressure, suppression of appetitite, stimulation of peristalsis and, with larger doses, nausea of central origin which may be associated with vomiting.

Nicotine is rapidly metabolized by man and certain other mammals. The primary pathway through (−)-cotenine to γ-(3-pyridyl)-γ-methylaminobutyric acid is described in detail. The known metabolites have very low toxicity.

The rapidity of degradation to non-toxic metabolites, the results from chronic studies on animals, and the low mortality ratios of pipe and cigar smokers when compared with non-smokers indicate that the chronic toxicity of nicotine in quantities absorbed from smoking and other methods of tobacco use is very low and probably does not represent a significant health problem.

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Chapter 8

Mortality

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PROSPECTIVE STUDIES OF MALE POPULATIONS

The principal data on the death rates of smokers of various types and of nonsmokers come from seven large prospective studies of men. In such studies, information about current and past smoking habits, as well as some supplementary information (e.g., on age), is first obtained from the members of the group to be studied. Provision is also made to obtain death certificates for all members of the group who die during subsequent years. From these data, over-all death rates and death rates by cause are computed for the different types of smokers, usually in five-year age classes.

These seven studies comprise all the large prospective studies known to us. The first started in October 1951: the latest, in October 1959.

In brief, the seven groups of men are as follows:

(1) British doctors, a questionnaire having been sent to all members of the medical profession in the United Kingdom by Doll and Hill, 1956 (5).

(2) White American men in nine states. These men were enrolled by a large number of American Cancer Society volunteers, each of whom was asked to have the questionnaire filled in by 10 white men between the ages of 50 and 69. Hammond and Horn, 1958 (10).

(3) Policyholders of U.S. Government Life Insurance policies, available to persons who served in the armed forces between 1917 and 1940. Dorn, 1958 (6).

(4) Men aged 35–64 in nine occupations in California who were suspected of being subject to a higher than usual occupational risk of developing lung cancer. Dunn, Linden and Breslow, 1960 (7).

(5) California members of the American Legion and their wives. Dunn, Buell and Breslow (8).

(6) Pensioners of the Canadian Department of Veterans Affairs, i.e., veterans of World Wars I and II and the Korean War. Best, Josie and Walker, 1961 (2).

(7) American men in 25 states, enrolled by volunteer researchers of the American Cancer Society, each of whom was asked to enroll about 10 families containing at least one person over 45. Hammond, 1963 (11).

It will be noted that the studies cover different types of population groups in three countries. Study (2), often referred to as the Hammond and Horn study, terminated after 44 months' follow-up, and the data discussed here for this study are essentially the same as those already published (10). All other studies have accumulated substantial amounts of data beyond that which has been published. The authors and agencies responsible for

the studies supplied their latest available data for this report. The tables in this Chapter are based on the new compilations.

Table I shows for each study the approximate number of subjects from whom usable replies about smoking habits were obtained, the date of enrollment, age range, number of months followed, total number of deaths, and the number of person-years of exposure. The number of subjects studied (usable replies) ranged from around 34,000 in the British doctors study to 448,000 in the new American Cancer Society study. The number of months of follow-up varied from about 22 to 120.

Although several of the studies obtained some data on women, only the California Legion study (8) and the new American Cancer Society study (11) include large numbers of women. No tabulations on women are as yet available from these prospective studies.

Data on Smoking History

The exact description of the type of smoking and the amount smoked at all times throughout a man's past life would necessitate an amount of detail and an accuracy of memory that was not considered practicable in these studies. While the information collected on smoking habits varied from study to study, all studies asked for data on the *current* amount and type of smoking as of the date of answering the questionnaire. These amounts were usually expressed as the number of cigarettes, cigars or pipes per day. In the case of subjects who had stopped smoking previous to the date of enrollment (ex-smokers), most studies obtained data on the maximum amount previously smoked per day. The category described as *non-smokers* sometimes included also those men who had smoked an insignificant total amount during their whole previous lifetime.

As regards type of smoking, cigarettes, cigars and pipes appear in all seven combinations. Since results for the "mixed" categories are difficult to interpret and sometimes involve relatively small numbers of subjects, the analysis here concentrates on the following types:

Cigarettes only
Cigarettes and other
Cigars only
Pipes only

In some instances the last two categories have been combined when the numbers of subjects are too small to give reliable data for the separate types.

Adjustment for Differences in Age Distribution

Since the death rate of any group of men is markedly affected by their age distribution, it is essential, when comparing the death rates of two groups of men, to ensure that their age distributions are comparable. A standard measure for this purpose is the *age-specific* death rate, in which the rate is computed for a group of men whose ages all lie within a relatively narrow span, say 50–54 years. This measure is particularly appropriate when it is desired to examine how the relative death rates in two groups change with age.

TABLE 1.—*Outline of prospective studies of smoking and mortality*

Authors	Doll & Hill (5)	Hammond & Horn (10)	Dorn (6)	Dunn, Linden, Breslow (7)	Dunn, Buell, Breslow (8)	Best, Josie, Walker (2)	Hammond (11)
Subjects	British doctors	White men in 9 States	U.S. veterans	California occupational groups	California American Legion members	Canadian pensioners (veterans and dependents)	Men in 25 States
Number of usable replies	34,000	188,000	248,000	67,000	60,000	78,000	448,000
Date of enrollment	Oct. 1951	Jan.–Mar. 1952	Jan. 1954 and Jan. 1957.	Nov. 1953 and May 1957.	May–Nov. 1957	Sept. 1955–July, 1956	Oct. 1959–Feb. 1960.
Age range	35–75+	50–69	30–75+	35–69	35–75+	35–75+	35–89
Months followed	120	44	78	About 48	About 24	72	About 22
Number of deaths	4,534	11,870	24,519	1,714	1,704	9,070	11,612
Person-years of exposure	289,000	668,000	1,312,000	222,000	119,000	383,000	820,000

Several methods of adjustment for differences in age distribution are available for populations that have a wide range of ages. For comparing the death rate of a group of smokers with that of the non-smokers in the study, the measure most frequently used in previous publications is a type of *mortality ratio*, obtained as follows: In each five-year age class, the age-specific death rate for non-smokers is multiplied by the number of person-years in the group of smokers. This product gives an expected number of deaths, which represents the number of deaths of smokers that would be expected to occur if the age-specific death rate were the same as for non-smokers. These expected numbers of deaths are added over all age classes, and their total is compared with the total number of observed deaths in the smokers. The mortality ratio is the ratio (total observed deaths in the smokers)/(total expected deaths). A mortality ratio of 1 implies that the over-all death rates are the same in smokers and non-smokers after this adjustment for differences in age distribution. It does not imply that the death rates of smokers and non-smokers were the same at each specific age. A mortality ratio higher than 1 implies that the group of smokers has a higher over-all death rate than the non-smokers.

Another common method of adjustment for age is to use some age-distribution as a standard, for instance the combined age-distribution of all persons in the study or the age-distribution of the U.S. male population as of a certain Census year. The age-specific death rates for a certain group (e.g., smokers) are multiplied by the number of persons of that age in the standard distribution. These products are added and finally divided by the total standard population to obtain an *age-adjusted* rate for the group. A mortality ratio of smokers to non-smokers is then computed as the ratio of the age-adjusted rates for smokers and non-smokers. Mortality ratios computed in different ways will of course give somewhat different results and experts in this field do not regard any one method as uniformly best. In this report we have used the ratio of observed to expected deaths, as described in the previous paragraph, primarily because this measure is the most common one in previous publications from these studies. Both methods of adjustment run the risk of concealing a change in the relative death rate with age. For instance, the over-all mortality ratio might be unity if smokers had higher death rates than non-smokers prior to age 60, but lower death rates thereafter.

Smokers and non-smokers may differ with regard to variables other than age that are known or suspected to influence death rates, such as economic level, residence, hereditary factors, exposure to occupational hazards, weight, marital status, and eating and drinking habits. In the summary results to be presented in subsequent sections, as in most results previously published, the death rates of smokers and non-smokers have not been adjusted so as to equalize the effects of these disturbing variables. This issue will be discussed later in this chapter.

A further complexity in interpreting the results comes from interrelationships among the variables that describe the habit of smoking. As will be seen, the death rates of a group of cigarette smokers vary with the amount smoked, the age at which smoking was started, the duration of smoking, and the amount of inhalation. In trying to measure the "net" effect of one of these variables, such as the number of cigarettes smoked per day, we

should make adjustments so that the different groups of smokers being compared are equalized on all other relevant aspects of the practice. This can be done at best only partially. Most studies measured only some of the variables on which adjustment is desirable. When the data are subclassified in order to make the adjustments, the numbers of deaths per subclass are small, with the consequence that the adjusted death rates are somewhat unstable.

Consequently, like previous reporters on these studies, we have used our judgment as to the amount of subclassification and adjustment to present. The possibility that part of the differences in death rates may be associated with smoking variables other than the one under discussion cannot be excluded.

RESULTS FOR TOTAL DEATH RATES

Mortality Ratios for Current Smokers

Table 2 shows the mortality ratios to non-smokers for men who were smoking regularly at the time of enrollment.

For males smoking cigarettes only, the over-all death rate is higher than that for non-smokers in all studies, the increase ranging from 44 percent for the British doctors to 83 percent in the men in 25 states. For smokers of other forms of tobacco as well as cigarettes the increases in death rates are in all cases lower than for the smokers of cigarettes only.

For smokers of cigars only or of pipes only, three of the studies show small increases in over-all death rates, ranging from 5 percent to 11 percent. The study of men in 25 states, however, gives slight decreases for both types, as does the British study for the two types combined.

TABLE 2.—*Mortality ratios of current smokers by type of smoking*

Type of smoking	Study group[1]				
	British doctors	Men in 9 States	U.S. veterans	Canadian veterans	Men in 25 States
Cigarettes only	1.44	1.70	1.79	1.65	1.83
Cigarettes and other	1.05	1.45	1.66	1.23	1.34
Cigars only	0.95	1.10	1.07	1.11	0.97
Pipes only		1.05	1.08	1.10	0.86

[1] The California occupational and Legion studies give mortality ratios of 1.78 and 1.38 respectively, for all cigarette smokers (current and ex-smokers).

Mortality Ratios by Amount Smoked

For smokers of cigarettes only who were smoking at the time of entry, the mortality ratio increases consistently with the amount smoked in each of the seven studies, with one exception for the California occupational study, which includes ex-cigarette smokers as well as current smokers (Table 3).

For smokers of cigars only who were smoking at the time of entry, four of the studies give a breakdown into two amounts of smoking (Table 4).

Men smoking less than five cigars per day have death rates about the same as non-smokers. For men smoking higher amounts there is some elevation of the death rate. When the results are combined by adding the observed and expected deaths over all four studies, an over-all mortality ratio of 1.20 is obtained for the five-or-more group. This over-all increase is statistically significant at the 5 percent level.*

TABLE 3.—*Mortality ratios for current smokers of cigarettes only, by amount smoked*

Cigarettes per day	British doctors	Men in 9 States	U.S. veterans	California occupational[1]	California Legion[2]	Canadian veterans	Men in 25 States
Less than 10	1.06	1.33	1.35	1.44	[3] 1.30	1.55	1.45
10-20	1.31	1.66	1.76	1.79		1.68	1.75
21-39	[4] 1.62	1.93	1.99	2.27	[5] 1.64	[6] 1.84	1.90
40 and over	[7] 2.50	2.20	2.22	1.85	[8] 1.85		2.20

*Current and ex-cigarette smokers combined.
[1] "Less than 10" is "less than 5" plus "about 5½"; "10-20" is "about 1"; "21-39" is "about 1½".
[2] Less than 1 pack.
[3] 20-34.
[4] 35 plus.
[5] More than 1 pack.
[6] About 1 pack.
[7] More than 1 pack.

TABLE 4.—*Mortality ratios for current smokers of cigars only, by amount smoked*

Number per day	Men in 9 States	U.S. veterans	Canadian veterans	Men in 25 States	Over-all results
1-4	1.06	0.99	[1] 1.12	0.93	1.00
5 or more	1.20	1.24	[2] 1.26	1.10	1.20

[1] 1-2.
[2] 3 or more.

For current pipe smokers (Table 5), men smoking less than 10 pipefuls per day have death rates very close to those of non-smokers. For heavy pipe smokers (10 or more per day) two studies show increases of 15 and 12 percent in death rates, but the other two studies show little or no increase. The over-all mortality ratio of 1.05 does not differ statistically from unity. The

*Statistical significance throughout this report refers to the 5 percent level unless otherwise specified. In testing whether an observed mortality ratio of smokers relative to non-smokers is greater than unity, the probability is calculated that a ratio as large as or larger than the observed ratio would occur by chance if the smokers and non-smokers were drawn from two populations having the same death rate. If this probability is less than 0.05 (5 percent) the observed increase in the death rate of smokers relative to non-smokers is said to be statistically significant at the 5 percent level. The results of significance tests will be quoted only for mortality ratios in which the number of deaths raises a doubt as to whether the difference from unity could be due to sampling errors.

British doctors study gives a mortality ratio of 0.91 for cigar and pipe smokers together (presumably mostly pipe smokers) who consume more than 14 gms. of tobacco daily.

TABLE 5.—*Mortality ratios for current smokers of pipes only, by amount smoked*

Pipes per day	Study				Over-all ratio
	Men in 9 States	U.S. veterans	Canadian veterans	Men in 25 States	
1–9	1.00	1.03	1.07	0.92	1.01
10 or more	1.15	1.12	1.01	0.76	1.05

MORTALITY RATIOS AT DIFFERENT AGES

As indicated previously, the mortality ratios presented in previous tables for different groups of smokers represent a kind of average over the age-distribution of the smokers concerned, and do not necessarily apply to smokers of any specific age. For cigarette smokers, the studies show that the mortality ratio declines with increasing age, being higher for men aged 40–50 than for men over 70. This effect is illustrated in Table 6 from the study of men in 25 states, which gives the mortality ratio computed separately for five age classes.

The drop in mortality ratio with each increase in age appears fairly consistently for every amount of smoking. For smokers of cigarettes only as a whole, the death rate is more than double that for non-smokers in the age range 40–49, but only about 20 percent higher for men over 80. The picture is, of course, different if we look at the *absolute* excess in death rates at different ages. Owing to the marked increase in death rates with age, the absolute excess also increases steadily with increasing age.

A more thorough investigation of the relation between death rates and age for different groups of smokers has been made by Ipsen and Pfaehler (14). If the logarithm of the age-specific death rate is plotted against age, the resulting points lie reasonably close to a straight line. For the U.S.

TABLE 6.—*Mortality ratios by age group for current smokers of cigarettes only, men in 25 States*

Number of cigarettes per day	Age at start of study				
	40–49	50–59	60–69	70–79	80–89
1–9	2.27	1.44	1.40	1.40	1.08
10–19	2.13	1.94	1.69	1.50	1.63
20–39	2.22	2.05	1.78	1.43	1.18
40+	2.06	2.37	1.69	1.38	0.88
All amounts	2.23	2.06	1.70	1.47	1.22

veterans study, Figure 1 shows the points and fitted lines for non-smokers and for current smokers of cigarettes only. (The lines were fitted by the standard method of least squares, weighting each point by the number of deaths involved.)

If the lines for cigarette smokers and non-smokers were parallel, this would imply that the mortality ratio of the smokers to the non-smokers was constant at all ages, because the vertical distance between the two lines at any age is the log of the mortality ratio for that age. In Figure 1, however,

DEATH RATE (logarithmic scale) PLOTTED AGAINST AGE, PROSPECTIVE STUDY OF MORTALITY IN U.S. VETERANS

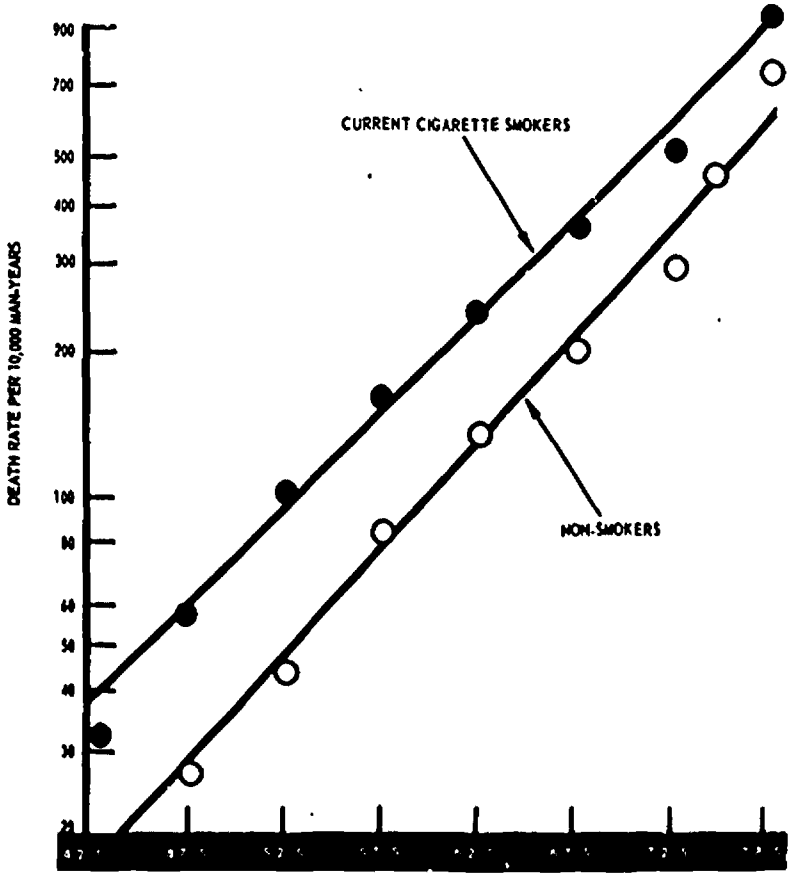

FIGURE 1.

the slope is slightly less steep for the cigarette smokers than for the non-smokers. This indicates that the mortality ratio is declining with increased age.

Table 7 shows these slopes (increase in the *natural* logarithm of the death rate for each 5-year increase in age) computed from six of the studies. The salient features are as follows: (1) In each study the slope for cigarette smokers is smaller than the slope for non-smokers; (2) Within the cigarette smokers the slope tends to decline, with some inconsistencies, as the amounts smoked become greater; (3) for cigar or pipe smokers the slopes are closer to those for non-smokers.

TABLE 7.—*Increase in natural logarithm of death rate per 1,000 man-years for each 5-year increase in age, 6 prospective studies*

Type of smoking	British doctors	Men in 9 States	U.S. veterans	California occupational [1]	California Legion [1]	Men in 25 States [2]
Non-smokers	.503	.474	.499	.489	.502	.490
Cigarettes by amount per day	.492	.427	.448	.436	.476	.438
1-9	.536	.484	.490	.401	.567	.445
10-20	.551	.457	.454	.461	.471	.441
21-39	.477	.420	.467	.447	.449	.401
40+	.401	.345				.401
Cigars	.678	.466	.483			.457
Pipes		.321	.458			.458

[1] "Cigarettes" includes "cigarettes and other" and current and ex-smokers.
[2] First 10 months' experience.

AGE AT WHICH SMOKING WAS STARTED

The study of U.S. veterans and the study of men in 25 states provide data on the death rates of current smokers of cigarettes only, classified by the age at which the person started to smoke. Since in both studies the men who start to smoke early tend to smoke greater amounts per day than men who start later in life, the mortality ratios to non-smokers are presented separately for different amounts of smoking (Table 8).

TABLE 8.—*Mortality ratios by age at which smoking was started and by amount smoked for current smokers of cigarettes only*

Age started to smoke	Number of cigarettes per day				Over-all ratio
	1-9	10-20	21-39	40+	
U.S. veterans:					
Under 20	1.80	1.88	2.16	2.45	1.98
20-24	1.60	1.73	1.87	2.23	1.73
25 or over	1.18	1.30	1.47	1.11	1.39
Men in 25 States:					
Under 15	1.79	[1] 2.23	[2] 2.21	2.15	2.17
15-19	1.75	[1] 1.83	[2] 2.01	2.38	1.99
20-24	1.35	[1] 1.52	[2] 1.63	1.98	1.54
25 or over	1.08	[1] 1.26	[2] 1.45	1.36	1.34

[1] 10-19 cigarettes per day.
[2] 20-39 cigarettes per day.

For a fixed amount of smoking, the mortality ratios (with one exception) exhibit a consistent and rather striking increase as the age at which smoking was started decreases. This increase appears in all smoking groups of Table 8. For men who started smoking cigarettes under the age of 20, the over-all death rate was about twice that for non-smokers, whereas for those who did not start until they were over 25 the death rate was only about 35 percent higher.

Mortality Ratios by Duration of Smoking

Three studies have some data available on the number of years during which the subjects had smoked. The comparison of mortality ratios for different lengths of time smoked is of interest in relation to two questions raised by Dorn (6) in an earlier analysis of the U.S. veterans' data. Is there a minimum period of use during which no effect on the death rate is noticeable? Is there a maximum period after which no increase in the relative death rate is perceptible?

For current cigarette smokers the results (Table 9) are not clear-cut. In the U.S. veterans study, men smoking for less than 15 years had death rates about the same as non-smokers. There is a rise of about 50 percent in the mortality ratio for those who had smoked 15–35 years, with a further rise for those smoking longer than 35 years. The study of men in nine states shows a rise from under 25 years to 25–34 years duration, but no further rise thereafter. In the Canadian study the mortality ratio with cigarette smokers is just as high for durations less than 15 years as for durations of 15–29 years, though there is a rise (to 1.73) for smokers of cigarettes only who have been smoking more than 30 years.

Table 9.—*Mortality ratios for current smokers by type of smoking and by length of time smoked*

Type of smoking	Number of years smoked									
	U.S. veterans				Canadian veterans			Men in 9 States		
	<15	15–24	25–34	35+	<15	15–29	30+	<25	25–34	35+
Cigarettes only	0.92	1.53	1.80	1.88	1.53	1.41	1.73	1.46	1.74	1.78
Cigarettes and other	1.07	1.41	1.53	1.69	1.24	1.27	1.22	.....	.....	.....
Cigars only	0.92	0.94	0.95	1.17	1.06	0.81	1.31	.....	.....	.....
Pipes only	1.01	1.34	0.97	1.07	1.36	0.98	1.09	.....	.....	.....

Thus, all three studies show some increase in the mortality ratios with longer duration of smoking, but the pattern is irregular. In a further breakdown of the data by amount smoked, Hammond and Horn (10) found no trend with duration for men smoking more than a pack a day, but the other two studies show an upward trend for this group of smokers.

For cigar smokers the only groups showing an increase in death rates over non-smokers are those smoking for the longest period (Table 9). The increases of 12 percent for the 35 years or over group in the U.S. study and of

31 percent for the 30 years or over group in the Canadian study are both statistically significant.

For pipe smokers no trend with duration of smoking is discernible. The two figures which stand out (1.34 in the U.S. study and 1.36 in the Canadian study) are both based on relatively small numbers of deaths.

Inhalation of Smoke

In two of the studies the subjects were questioned as to whether they inhaled. In the study of men in 25 states each subject was asked to place himself in one of the four classes: do not inhale, inhale slightly, inhale moderately, inhale deeply. In the Canadian veterans study the subject simply classified himself as an inhaler or non-inhaler.

For current smokers of cigarettes only in the U.S. study, 6 percent of the subjects stated that they *did* not inhale, 14 percent inhaled slightly, 56 percent moderately and 24 percent deeply. In the Canadian study 11 percent classified themselves as non-inhalers.

Since inhalation practices may vary with the amount smoked, the results for cigarette smokers (Table 10) are given separately for different amounts. For the men in 25 states an increase in the degree of inhaling for a fixed amount of smoking is in general accompanied by an increase in the mortality ratio. The relation of inhalation to mortality appears quite marked: for instance, non-inhalers who smoke 20–39 cigarettes daily have mortality ratios no higher than moderate or deep inhalers who smoke 1–9 cigarettes daily. With the very heavy smokers (40+) the figures in Table 10 suggest that the mortality ratio may remain the same for non-, slight, and moderate inhalers. The ratios of 2.05 (non-) and 1.97 (slight) are, however, based on only 26 and 41 deaths, respectively.

TABLE 10.—*Mortality ratios for smokers of cigarettes only by inhalation status and amount of smoking*

Degree of inhalation	Cigarettes per day				Over-all ratio
	1-9	10-19	20-39	40+	
Men in 25 States:					
None	1.29	1.46	1.56	2.05	1.49
Slight	1.29	1.66	1.94	1.97	1.69
Moderate	1.61	1.83	1.94	2.01	1.83
Deep	1.88	1.76	2.15	2.30	2.20
Canadian veterans: [1]					
None	1.05	[2] 1.11	[3] 1.03	.....	1.06
Some	1.35	[2] 1.30	[3] 1.71	.....	1.53

[1] Amounts are lifetime maximum amounts smoked.
[2] 10-20 cigarettes per day.
[3] Over 20 cigarettes per day.

Looking along the rows of the U.S. veterans study it will be seen that for each degree of inhalation the mortality ratio increases with the amount smoked. Ipsen and Pfaelzer (14) have shown that the logarithms of the 16 death rates at age 61 (approximately the average age) can be adequately rep-

resented as an additive function of the amount of smoking and the degree of inhalation (although other types of mathematical relationship would also fit the data). In their analysis, the average change in logarithm of death rate from "no inhalation" to "deep inhalation" is as great as the difference between consumption of less than 10 cigarettes and consumption of more than 40 cigarettes daily.

In the Canadian data the inhalers have higher mortality ratios than the non-inhalers for each amount of smoking. No trend with amount of smoking appears for the non-inhalers, but the ratios in this row are based on rather small numbers of deaths.

For cigar smokers (current and ex-smokers) in the 25-state study 19 percent stated that they inhaled to some extent. The mortality ratio is 0.89 for non-inhalers and 1.37 for inhalers. The latter increase of 37 percent (based on 91 deaths) is statistically significant, but as the data have not been subclassified by amount of smoking the result may be partially a reflection of the increase in death rates noted in Table 4 for heavy cigar smokers. In the Canadian study, 13 percent of the cigar smokers classified themselves as inhalers, but the number of deaths is insufficient to present a breakdown of the mortality ratio by inhalation status.

Among the pipe smokers there were 28 percent who inhaled in the U.S. study and 18 percent in the Canadian study. The U.S. mortality ratios are 0.8 for non-inhalers and 1.0 for inhalers; the Canadian data contain too few deaths to allow a breakdown by inhalation.

Ex-Cigarette Smokers

For men who had stopped smoking prior to the date of enrollment, Table 11 gives the mortality ratios from five studies for "cigarette only" smokers and "cigarette and other" smokers. The corresponding results for current cigarette smokers (from Table 2) are given for comparison. The distinction between current and ex-smokers is not of course clear cut, since some current smokers may have stopped after enrolling in the study and some ex-smokers may have later resumed smoking.

With one exception, the mortality ratios for ex-smokers lie consistently below those for current smokers and above those for non-smokers. In interpreting comparisons of ex-smokers and current smokers there are at least three relevant factors. If smoking is injurious to health, cessation of smoking would be expected to reduce the mortality ratio. Secondly, some men stop smoking because of illness. In the 25-State study, over 60 percent of the men who had stopped smoking within a year prior to entry stated that a disease or physical complaint was one of the reasons for stopping (12). This factor would tend to make mortality ratios for ex-smokers higher than those for current smokers. Finally, ex-smokers may have previously smoked smaller amounts than current smokers. This factor is not the explanation of the drops in mortality ratios in Table 11. In a further breakdown by amount of smoking, made for the three largest studies, the mortality ratio for ex-smokers is consistently below that for current smokers for each amount smoked.

TABLE 11.—*Mortality ratios for ex-smokers and current smokers of cigarettes*

	British doctors	Men in 9 States	U.S. veterans	Canadian veterans	Men in 25 States
Ex-cigarettes	1.04	1.40	1.41	1.42	1.50
Current cigarettes	1.44	1.70	1.79	1.65	1.83
Ex-cigarettes and other	1.21	1.29	1.21	1.18	1.51
Current cigarettes and other	1.05	1.45	1.46	1.23	1.54

TABLE 12.—*Mortality ratios for ex-smokers of cigarettes only by number of years since smoking was stopped and by amount smoked*

Study	Cigarettes per day	Number of years stopped					Current smokers
		<1	1-4	1-9	5-9	10+	
Men in 9 States [1]	<19	2.04	.....	1.30	.....	1.08	1.61
	20+	2.69	.....	1.82	.....	1.50	2.02
Men in 25 States	<19	1.60	1.62	.....	1.46	0.81	1.73
	20+	2.80	2.01	.....	1.51	1.22	2.01

[1] These data are from Hammond and Horn, 1958.

TABLE 13.—*Mortality ratios for ex-cigarette smokers by number of years of smoking, U.S. veterans study*

Cigarettes per day	Number of years of smoking			
	<15	15-24	25-34	35+
1-20	1.05	1.08	1.25	1.56
20+	1.12	1.18	1.41	2.00
	Age at which smoking was stopped			
	<45	45-54	55+	
1-20	1.03	1.34	1.51	.....
20+	1.12	1.59	1.86	.....

Some supplementary analyses throw a little further light on this topic. In the two American Cancer Society studies (Table 12) a breakdown is given by the number of years since smoking was stopped.

Except for the smokers of under one pack a day in the 25-State study, the mortality ratio for men who had stopped less than a year is higher than that for current smokers. Thereafter the ratio drops steadily as the interval since smoking was stopped increases.

In the U.S. veterans study, further breakdowns are available by the numbers of years during which the ex-smokers were smoking and by the age at which smoking was stopped (Table 13), as well as by the amount of smoking. The mortality ratios are about the same for those smoking less than 15 years as for those smoking 15–24 years. Thereafter the ratios rise with longer durations of smoking. Table 13 also shows that mortality ratios were higher for those who stopped smoking at later ages.

Ex-Cigar and Pipe Smokers

Mortality ratios for smokers of cigars only and pipes only who had stopped smoking prior to the date of entry are given in Table 14, the corresponding ratios for current smokers being included for comparison.

For ex-cigar smokers the mortality ratios are higher than those for nonsmokers and higher than those for current smokers in all four studies presented. The same is true for ex-pipe smokers with the exception of the Canadian study.

The interpretation of this result is not clear to us. According to Hammond and Horn (10) and Dorn (6), the explanation may be that a substantial number of cigar and pipe smokers give up because they become ill: some data from cigarette smokers that support this explanation have recently been analyzed by Hammond (12). Further analysis of the U.S. veterans data indicates that mortality ratios run highest in ex-smokers who smoked heavily and for a long time.

Table 14.—*Mortality ratios for ex-smokers of cigars only and pipes only and for current cigar and pipe smokers*

Type of smoker	British doctors	Men in 9 States	U.S. veterans	Canadian veterans	Men in 25 States
Ex-cigar		1.66	1.30	1.17	1.24
Current cigar		1.10	1.07	1.11	0.97
Ex-pipe	[1] 1.12	1.29	1.28	1.01	1.23
Current pipe	[1] 0.95	1.03	1.06	1.10	0.96

[1] Pipe and cigar combined.

EVALUATION OF SOURCES OF DATA

The Study Populations

Various reasons dictated the particular choices made of the seven study populations, considerations of feasibility playing an important role. None of the populations was designed, in particular, to be representative of the U.S. male population. Any answer to the question "to what general populations of men can the results be applied?", must involve an element of unverifiable judgment. However, three of the studies have populations with widespread geographic distribution within the United States, as do the British and Canadian studies within their respective countries. Taken as a whole, the seven populations offer a substantial breadth of sampling of the type of men and environmental exposures to be found in North America and Britain, as well as providing some variation in methodological approach, although the basic plan was similar in all studies.

The seven studies differ considerably in size. They vary also in the extent to which they are free from methodological weakness. The studies of men in nine states and men in 25 States, for instance, suffer from the difficulties

that the populations studied are hard to define, that the smokers and non-smokers were recruited by a large number of volunteer workers, and that completeness in the reporting of deaths was hard to achieve, since this depends on reports from the volunteers. On the other hand these studies have the advantage of being large and of having a broad geographic representation of the U.S. male population, while the second study is the only one that attempts to investigate many other relevant variables in which smokers and non-smokers may differ. In the California occupational study the focus of interest is occupational differences in lung cancer mortality, smoking history being recorded primarily in order to be able to adjust comparisons among different occupational groups for differences in amount smoked. In the analysis we have not attempted to rate the studies as to over-all quality or to assign differential weights to their results, except that in the smaller studies it is recognized that mortality ratios are subject to larger sampling errors. Our attitude is to attach importance only to results that appear to be generally confirmed by the studies.

Some idea of the relative death rates in these studies as compared with the 1960 white male population of the United States is given in Table 15, which shows the age-adjusted death rates for ages 35 and over, using the age distribution of the U.S. white male population as a standard. (The choice of 1960 for the comparison is arbitrary, but the white male rate changed little between 1955 and 1960.)

In all studies the death rates for non-smokers are markedly below those of U.S. white males in 1960. Even the smokers of one pack of cigarettes or more daily have death rates that average slightly below the U.S. white male figure. To some extent this is to be expected, since hospitalized and other seriously ill persons are not recruited in such studies. The sizes of the differences appear, however, surprising for the studies with United States populations. Hammond and Horn (10), in a special investigation on this question, concluded that the discrepancy in their study was due to the screening out of sick persons in recruiting plus probably a selection towards men of higher economic levels. They point out that their death rates are substantially above those for males who had held ordinary life insurance policies for from

TABLE 15.—*Age-adjusted death rates per 1,000 man-years for current smokers of cigarettes only (aged 35 and over), by amount smoked, in seven studies and for U.S. white males*

Study	Non-smokers	Current smokers of cigarettes only		U.S. white males, 1960
		Less than 1 pack	1 pack or more	
British doctors	13.5	18.9	20.2	22.9
Men in 9 States	[1] 14.4	[1] 22.4	[1] 27.1	[1] 22.6
U.S. veterans	12.6	18.1	23.9	22.9
California occupational	[1] 10.5	[1] 16.9	[1] 18.9	[1] 22.6
California legion	11.3	16.4	16.3	22.9
Canadian veterans	14.1	22.1	24.2	22.9
Men in 25 States	[1] 12.9	[1] 18.5	[1] 19.9	22.9

[1] Ages 30-69.
[2] These figures may be too low by about 1.7 percent, since the person-years used in the computation included some contribution by men who had not been fully traced.

5 to 15 years. The U.S. veterans' study population also came mainly from the middle and upper socio-economic classes (6).

Another reason might be a failure to trace all deaths. In mass studies it is almost impossible to devise infallible provisions for recording every death. The study directors were, however, experienced in handling this problem and it seems unlikely that more than, say, 5 percent of the deaths would be missed. (Moreover, in the studies of veterans it is to the family's advantage to report the death.)

Another contribution probably came from the failure to obtain data for some members of the population. Evidence on this point is available from the British doctors and the U.S. veterans' studies, in which death rates for the complete population (respondents and non-respondents) are available. In these studies the death rate for the whole population exceeded that in the respondents, but by only 5 percent to 10 percent, so that non-response appears unlikely to be a major cause of the discrepancy.

So far as interpretation of results is concerned, the discrepancy raises two points. It is clear that the seven prospective studies involve populations which are healthier than U.S. males as a whole. Secondly, the low death rates for non-smokers suggest the possibility that the studies recruited unusually healthy groups of non-smokers. In the case of the five studies which had clearly defined populations, this selection would arise only if the non-smokers who refused to enter the study had death rates much higher than those who were enrolled. This point is discussed in the next section.

Non-Response Bias

In all five studies that had a clearly defined target population, sizeable proportions of the population were omitted. The major reason was failure to answer the questionnaire; in addition, certain replies were rejected as too incomplete. The percentages of the populations for which usable replies were obtained were approximately as shown in Table 16

Table 16.—*Percentages of usable replies in*

British doctors	U.S. veterans	California occupational	California Legion	C... v
68	68, 85	85	56	

In the U.S. veterans study, 68 percent replies ... from the 1954 questionnaire. A second questionnaire, sent in 19 ... an additional 17 percent, for whom data are available duri... 1957–60. In the two American Cancer Society studies it is ... to present meaningful percentages, since each research volunt... her own small part of the study population from among her ac...

The possible effects of these amounts of non-resp... nortality ratios have received little discussion. Some piece... ...ation about

non-respondents are available in two studies. From a recent sample, Doll (4) states that (a) the death rate of non-respondents in the British doctors study is higher than that of respondents; (b) consequently the death rate for respondents is lower than that of British doctors as a whole, perhaps by as much as 5 percent to 10 percent; (c) there are relatively more smokers among the non-respondents than among the respondents. In the U.S. veterans' study, the death rate for the whole study population exceeded that for the original 68 percent responders by 7 percent in 1958 and 5 percent in 1959. From this study one can also calculate mortality ratios separately, during 1957–60, for the 1954 respondents and the 1957 respondents. The results for smokers of cigarettes are as follows:

	1954 respondents (68 percent)	*1957 respondents (17 percent)*	*Non-respondents (15 percent)*
Current cigarettes only	1.87	1.71	?
Current cigarettes and other	1.56	1.33	?

Those who did not respond in 1954 but did respond in 1957 show lower mortality ratios than the original set of men giving usable replies. By making guesses about the mortality ratios in the 15 percent of non-responders, one can compare the resulting mortality ratio in the whole population with that found in the original 68 percent. To consider how much of an overestimate the ratios of 1.87 and 1.56 might be, we might suppose, to illustrate the method, that the mortality ratio is unity for the non-respondents. The mortality ratio for the whole population then turns out to be 1.71 for cigarettes only and 1.44 for cigarettes and other. Thus, with a non-response rate of 30 percent, the computed mortality ratio might overestimate by 0.1 or 0.2.

Berkson (1) produced a set of assumptions under which, with a mortality ratio of 1 in the whole population and a response rate of 71 percent, the mortality ratio in the respondents is found to be 1.5. Non-respondents are assumed to be of two types. One group, destined to have a high death rate, refuses because they don't feel well. This group has a high refusal rate (50 percent) for both smokers and non-smokers, since the reason for refusal is illness and not smoking. In the remainder of the non-respondents, the refusal rate is higher among smokers than non-smokers. Qualitatively, these assumptions are not unreasonable and agree in direction with the results quoted previously for the British doctors and U.S. veterans' studies. Korteweg (15) worked further examples of Berkson's model as applied to individual causes of death in the first report of the study of men in nine states. He concluded that the response bias in the mortality ratio might be as high as 0.3. Both Berkson and Korteweg, had, of course, to make some arbitrary assumptions about the sizes of biases from different sources.

Further discussion of the non-response bias and computations as to its magnitude are given in Appendix I. The computations indicate that reported mortality ratios lying between 1 and 2 might overestimate by as much as 0.3, a mortality ratio of 5.0 might overestimate by 1.0, and one of 10.0 might overestimate by 3.0. Thus, under assumptions that are rather extreme, although consistent with the available data about non-respondents,

the mortality ratios of cigarette smokers would still remain substantially higher than unity after adjustments for these amounts of over-estimation.

Measurement of Smoking History

Measurement of the type and amount of smoking, being based on a single mail questionnaire, was admittedly crude. Consider men recorded as current smokers of cigarettes only. Subsequent to enrollment, some of these presumably stopped smoking, at least temporarily, and some took up other forms, with or without cigarettes.

Similarly, some men recorded as non-smokers may have begun to smoke cigarettes subsequently. Consequently, the group designated as "current smokers of cigarettes only" presumably contained men who were, for some period of time "ex-smokers" or "cigarette and other" smokers, while men designated as "non-smokers" contained some who smoked cigarettes for a time. It seems likely that this dilution of the contrast between the two groups would make the mortality ratio of cigarette smokers, as reported in previous tables, underestimate the mortality ratio of unchanging cigarette smokers relative to unchanging non-smokers, particularly when we note that the groups labeled "ex-smokers of cigarettes" and "cigarette and other" smokers both had mortality ratios lower than the group labeled "current smokers of cigarettes only".

As regards number of cigarettes per day, two types of errors of measurement may occur. There will be "random" errors of measurement (some men overestimate the amount and others underestimate it) that tend to cancel out over all men in the study. The effect of such errors is that the reported data underestimate the increase in the mortality ratio per additional cigarette smoked daily, the computed increase being an estimate of $B/(1+h)$, where B is the true increase and h is the ratio of the variance due to errors of measurement in the amount smoked to its total variance, Yates (17). There may also, however, be systematic errors in reporting the amount smoked. Heavy smokers may tend to underestimate the amount smoked. If this happens, the reported increase in mortality ratio per additional cigarette smoked will be an overestimate of the true increase, although the upward trend of mortality ratio with increasing amount smoked will remain.

On balance, we are inclined to agree with the opinion expressed by the authors of several of the studies to the effect that the general result of errors in reporting smoking history is to depress the mortality ratios of smokers relative to non-smokers, so that reported ratios will tend to be underestimates so far as this source of error is concerned.

Stability of the Mortality Ratio

The sampling distribution of the mortality ratio has not to our knowledge been at all thoroughly investigated and appears to be complicated. As a rough approximation (Appendix II), the ratio of smoker deaths to smoker

plus non-smoker deaths may be regarded as a binomial proportion with mean $\lambda R/(1+\lambda R)$ where R is the true mortality ratio, λ is the ratio of the expected smoker deaths to the observed non-smoker deaths and the sample size is the number of smoker plus non-smoker deaths. From this approximation, confidence limits for R may be derived. This approximation requires that (1) the age distributions of smokers and non-smokers do not differ greatly and (2) all age-specific death rates are small. An alternative normal approximation that avoids assumption (1) is also given in Appendix II.

The sampling variation of the estimate of R is seldom of major import in this part of the report, since the ratios for total mortality are mostly based on relatively large numbers of deaths. The estimate has a positive mathematical bias, negligible with large but not with small numbers of deaths. In another sense the particular mortality ratio used in this report has a different kind of bias. Since the standard age-distribution used in this ratio is the age-distribution of the smokers, who are somewhat younger than the non-smokers, the mortality ratios apply to populations slightly younger than the combined population of the study. This is not in our opinion a serious objection, but may sometimes be relevant in questions of interpretation.

OTHER VARIABLES RELATED TO DEATH RATES

As mentioned previously, the smokers and non-smokers in these studies may differ with respect to other variables that might influence the death rate. Except in the new 25-State study, no attempt was made to measure these variables apart from urban-rural residence, and previous reports on these studies give little discussion of this problem. For urban-rural residence, Doll and Hill (5) found that the proportions of smokers of different amounts in the study population were about the same in rural areas, small cities and large cities. In three studies the mortality ratios of cigarette smokers were computed separately by size of city (6, 10, 11). In the study of men in 25 States, the data refer to men who smoked 20 or more cigarettes a day and said that they inhaled moderately or deeply. In all three studies the mortality ratios show little change with size of community (Table 17).

In the 25-State study, over 20 other variables that may be associated with death rates were recorded. The study population was broken down into subgroups for many of these variables separately: for instance, into smokers who have long-lived parents and grandparents and those whose parents and

TABLE 17.—*Mortality ratios for cigarette smokers by population-size of city*

Study	Population-size			
	Over 50,000	10,000–50,000	Small towns	Rural
Men in 9 States	1.48	1.62	1.50	1.52
U.S. veterans	1.54	1.51	1.42	1.59
Men in 25 States	1.89	[1] 2.02	.....	1.74

[1] Includes towns of less than 10,000.

grandparents were short-lived. Included among these variables were religion, educational level, native or foreign birth, residence by size of town and occupational exposure, use of alcohol, use of fried food, amount of nervous tension, use of tranquilizers, and presence or absence of prior serious disease. For cigarette smokers who smoked more than a pack a day and inhaled moderately or deeply, the mortality ratio was computed within each subgroup. For example, the mortality ratio was 1.99 for men with long-lived parents and 2.30 for men with short-lived parents. In every subgroup the mortality ratio was well above unity, the lowest among 71 computed ratios being 1.57 (for men with a history of previous serious disease).

These data provide information on the association of the other variables with mortality as well as on the association of smoking with mortality. For six of the most relevant variables, Table 18 gives age-adjusted death rates, using the combined populations of non-smokers and cigarette smokers as the standard population. The death rates apply to a period of roughly 22-months follow-up. As already mentioned, the cigarette smokers (of more than a pack per day who inhaled moderately or deeply) have higher death rates than the non-smokers in every cell of Table 18. Since not all respondents answered these supplementary questions, the results may be subject to some additional non-response bias.

As would be expected, death rates are relatively high for men with previous serious disease and for men from short-lived families, and are somewhat

TABLE 18.—*Age-adjusted death rates per 1,000 men (over approximately 22 months) for variables that may be related to mortality*

Type of smoking	Long-lived parents and grandparents	Short-lived parents and grandparents	No previous serious disease	Previous serious disease
None	14.8	21.1	11.5	42.5
Cigarettes [1]	27.1	44.8	22.3	65.0
	Single	Married	Use tranquilizers	Do not use tranquilizers
None	26.0	18.9	29.1	18.2
Cigarettes [1]	50.1	33.0	52.4	31.8
	Educational level			
	No high school	Some high school	High school graduate	Some college	College graduate
None	22.7	20.0	16.9	18.3	15.8
Cigarettes [1]	35.2	34.5	35.5	34.2	29.4
	Degree of exercise [2]			
	None	Slight	Moderate	Heavy
None	23.8	14.7	11.0	9.5
Cigarettes [1]	34.1	25.5	20.8	19.7

[1] Smokers of more than a pack per day who inhaled moderately or deeply.
[2] Confined to men with no history of heart disease, stroke, high blood pressure or cancer (except skin) who were not sick at the time of entry.

higher for single than for married men. The size of the excess death rate for users of tranquilizers compared to men who do not use them is perhaps surprising (29.1 against 18.2 and 52.4 against 31.8). However, the tranquilizers in question required a doctor's prescription, so that some men in this group are presumably under medical attention for illness. The group of users is small, comprising only about 10 percent of those who answered this question. Death rates tend to decrease slightly as the educational level increases; this association may represent some facet of the association of death rates with socio-economic level. Degree of exercise displays an interesting association with mortality, the death rate declining steadily with additional degrees of exercise. In particular, the two "no exercise" groups show marked elevations in death rates. These groups, however, amount to only 2 percent of the respondents to this question.

From the same data, Ipsen and Pfaelzer (14) made a further analysis of seven variables that appeared to be related to mortality, in order to see whether any of the variables had a stronger association with mortality than did cigarette smoking. They concluded that apart from previous serious disease, none of the other variables examined had as high a correlation with mortality as smoking of cigarettes. Further, the correlation of any of these other variables with cigarette smoking was too weak to reduce markedly the correlation of cigarette smoking with mortality after adjustment for the other variable.

In the analyses above, smoking was matched against each variable separately. In addition, Hammond (11) carried out a "matched pair" analysis, in which pairs of cigarette smokers and non-smokers were matched on height, education, religion, drinking habits, urban-rural residence and occupational exposure. The percentage who had died in the 22 months was 1.64 for smokers and 0.88 for non-smokers.

These informative analyses are available, unfortunately, for only one of the studies. However, in order that the association of cigarette smoking with mortality should disappear when we adjust for another variable, the correlations of this variable with smoking and with the death rate must both be higher than the correlation between smoking and the death rate.

Except for the breakdowns by longevity of parents and grandparents, the analyses throw little light, however, on the objection that a part of the differences in death rates may be constitutional, psychological or behavioral; i.e., that regular cigarette smokers are the kind of men who would have higher death rates even if they did not smoke. Further discussion of this point appears in the next section.

MORTALITY BY CAUSE OF DEATH

In all seven studies the underlying cause of death, as specified in the International Statistical Classification of Diseases, Injuries and Causes of Death, was abstracted from the death certificate. In the two American Cancer Society studies, further confirmation of the cause of death, including histological evidence, was sought from the certifying physician for all cancer deaths; this

procedure was also followed in the British doctors' study for all certificates in which lung cancer was mentioned as a direct or contributory cause. With these exceptions the data presented here represent the results of routine death certification.

For current smokers of cigarettes the total mortality, after adjustment for differences in age composition, was found previously (Table 2) to be about 70 percent higher than that of non-smokers in these studies. The primary objective in this section is to examine whether this percentage increase appears to apply about equally to all principal causes of death, or whether the relative increase is concentrated in certain specific causes or groups of causes.

Results for Cigarette Smokers

For 24 causes of death, plus the "all other causes" category, Table 19 shows summary data over all seven studies.* In four of the studies the data are those for current smokers of cigarettes only, but in the two California studies and the 25-State study the cause-of-death breakdown was available only for all cigarette smokers including "cigarette and other" smokers and current and ex-smokers.

For each listed cause, Table 19 shows the total numbers of expected and observed deaths of cigarette smokers summed over all seven studies, and

Table 19.—*Total numbers of expected and observed deaths and mortality ratios for smokers of cigarettes only* [1] *in seven prospective studies*

Underlying cause of death	Expected	Observed	Mortality ratio	Median mortality ratio	Non-smoker deaths
Cancer of lung (162-3)	170.3	1,833	10.8	11.7	123
Bronchitis and emphysema (502, 527.1) [2]	89.5	546	6.1	7.5	59
Cancer of larynx (161)	14.0	75	5.4	5.8	8
Cancer of oral cavity (140-8)	37.0	152	4.1	3.9	27
Cancer of esophagus (150)	33.7	113	3.4	3.3	19
Stomach and duodenal ulcers (540-1)	105.1	294	2.8	5.0	67
Other circulatory diseases (451-468)	254.0	649	2.6	2.3	170
Cirrhosis of liver (581)	169.2	379	2.2	2.1	96
Cancer of bladder (181)	111.6	216	1.9	2.2	92
Coronary artery disease (420)	6,430.7	11,177	1.7	1.7	4,731
Other heart diseases (421-2, 430-4)	526.0	868	1.7	1.5	398
Hypertensive heart disease (440-3)	409.2	631	1.5	1.5	334
General arteriosclerosis (450)	210.7	310	1.5	1.7	201
Cancer of kidney (180)	79.0	120	1.5	1.4	59
All other cancer	1,061.4	1,524	1.4	1.4	742
Cancer of stomach (151)	285.2	413	1.4	1.3	203
Influenza, pneumonia (480-493)	303.2	415	1.4	1.6	169
All other causes	1,508.7	1,946	1.3	1.3	1,036
Cerebral vascular lesions (330-4)	1,461.8	1,844	1.3	1.3	1,069
Cancer of prostate (177)	253.0	318	1.3	1.0	198
Accidents, suicides, violence (800-999)	1,063.2	1,310	1.2	1.3	627
Nephritis (592-4)	156.4	173	1.1	1.5	98
Rheumatic heart disease (400-416)	290.6	309	1.1	1.1	185
Cancer of rectum (154)	207.8	213	1.0	0.9	150
Cancer of intestines (152-3)	422.6	395	0.9	0.9	307
All causes	15,653.9	26,223	1.68	1.65	11,168

[1] Current cigarettes only for four studies: all cigarettes (current and ex-) for the two California studies and the study of men in 25 States.
[2] "Bronchitis and emphysema" includes "other bronchopulmonary diseases" for men in nine States and Canadian veterans.

*The individual results for the seven studies are shown for reference purposes in Table 26.

the resulting mortality ratios, arranged in order of decreasing ratios. The combination of the results of the seven studies in this way is open to criticism, since it gives more weight to the larger studies than may be thought advisable, and since the true mortality ratios for specific causes presumably differ somewhat from study to study. However, for some causes of death that are of particular interest the numbers of deaths are small in all studies, so that some procedure for combining the results is highly desirable. As an alternative measure of the combined mortality ratio, the median of the seven mortality ratios (obtained by arranging the seven ratios in increasing order and selecting the middle one) is also shown for each cause in Table 19. The median, of course, gives equal weight to small and large studies. Although there are some changes in the ordering of the causes when medians are used instead of the ratios of the combined deaths, the general pattern in Table 19 is the same for both criteria.

Table 19 also presents the total numbers of non-smoker deaths on which the combined mortality ratios are based.

Lung cancer shows the highest mortality ratio in every one of the seven studies, the combined ratio being 10.8. Other causes that exhibit substantially higher mortality ratios than the ratio 1.68 for all causes of death in Table 19 are bronchitis and emphysema, cancer of the larynx, cancer of the oral cavity and pharynx, cancer of the esophagus, stomach and duodenal ulcers, and a rather mixed category labeled "other circulatory diseases," which includes aortic aneurysm, phlebitis of the lower extremities, and pulmonary embolism. For three of these causes—cancer of the larynx, oral cancer and cancer of the esophagus—the numbers of non-smoker deaths are small, so that the over-all mortality ratio cannot be regarded as accurately determined.

The U.S. veterans' study and the 25-State study provide an additional breakdown for two of the causes listed in Table 19. For the rubric 527.1 (emphysema without mention of bronchitis), these studies give mortality ratios of 13.1 and 7.5, respectively. For ulcer of the stomach they give 5.1 and 4.3, whereas for ulcer of the duodenum their mortality ratios are 2.3 and 1.1. Bronchitis and emphysema also show a high rate, 12.5, in the British doctors' study.

There follows a list of 14 causes whose mortality ratios are not greatly different from the ratio of 1.68 for all causes in Table 19. These causes range from cirrhosis of the liver, with a ratio of 2.2, down to a ratio of 1.2 for the miscellaneous class which contains accidents, suicides and violent deaths. This group includes the leading cause of death, coronary artery disease, with a ratio of 1.7, cerebral vascular lesions with a ratio of 1.3, and the "all other causes" group with a ratio of 1.3. For each of these 14 causes the mortality ratio differs from unity, by the approximate statistical test of significance.

Finally, there are four causes—nephritis, rheumatic heart disease, cancer of the rectum and cancer of the intestines—whose mortality ratios are close to unity.

For smokers of cigarettes and other, the data from four studies agree in general with the ordering of causes in Table 19, although the mortality ratios for most causes are slightly lower than with smokers of cigarettes

only. These and the corresponding data for ex-cigarette smokers are shown in Table 20.

Data on ex-cigarette smokers can be obtained from four studies. The causes of death with mortality ratios of 2.0 or higher are, in decreasing order, bronchitis and emphysema (7.6), cancer of the larynx (5.4), cancer of the lung (4.8), stomach and duodenal ulcers (3.1), oral cancer (2.0), and other circulatory diseases (2.0).

The group of 17 causes with mortality ratios below 2 in Table 19 requires discussion. If cancer of the bladder (mortality ratio 1.9) and coronary artery disease (mortality ratio 1.7) are omitted, since they receive detailed consideration elsewhere in this report, the numbers of expected and observed deaths for this group as a whole are as follows:

Expected	*Observed*	*Mortality Ratio*
8,241.3	10,789	1.31

If we exclude from this total the four causes at the foot of Table 19, for which the mortality ratios are 1 and smaller, the corresponding totals become:

Expected	*Observed*	*Mortality Ratio*
7,164.0	9,699	1.35

In either case the excess of observed over expected deaths is close to 2,500 or about 25 percent of the total excess in observed deaths in Table 19. Thus, although the mortality ratios for these groups are only moderately over 1, the group as a whole contributes substantially to the total number of excess observed deaths. The group consists mainly of a miscellaneous collection of chronic diseases.

Several tentative explanations of this excess mortality ratio can be put forward. Part may be due to the sources of bias previously discussed. It was indicated in the section on "Non-Response Bias" that the bias arising from non-response might account for a mortality ratio of 1.3. Relatively high mortality ratios in certain causes of death that have not yet been examined individually may also be a contributor, although as these causes are likely to be rare, the contribution from this source can hardly be large.

Part may be due to constitutional and genetic differences between cigarette smokers and non-smokers. Except for the breakdown mentioned previously by longevity of parents and grandparents in the men in 25 States study, there is no body of data available that provides a comparison of cigarette smokers and non-smokers on these factors as they affect longevity. But it is not unreasonable to speculate that the kind of men who become regular cigarette smokers are, to a moderate degree, less inherently able to survive to a ripe old age than non-smokers. We know of no way to make a quantitative estimate of the difference in death rates that might be attributable to such constitutional and genetic factors.

Studies reported in Chapters 14 and 15 indicate that some average differences can be detected between smokers and non-smokers on behavioral, psychological and morphological characteristics. Nevertheless, the same comparisons show considerable overlap between the individual men in a group of smokers and a group of non-smokers. For what they are worth, these com-

TABLE 20.—*Expected and observed deaths and mortality ratios for current smokers of cigarettes and other (three studies)* [1] *and for ex-cigarette smokers (four studies)* [2]

Underlying cause of death	Cigarettes and other			Ex-cigarette		
	Number of deaths		Mortality ratio	Number of deaths		Mortality ratio
	Expected	Observed		Expected	Observed	
Cancer of lung (162-3)	60.9	510	8.4	30.4	145	4.8
Bronchitis and emphysema (502, 527.1) [3]	53.2	191	3.6	17.4	133	7.6
Cancer of larynx (161)	1.6	20	12.5	1.3	7	5.4
Cancer of oral cavity (140-8)	11.1	42	3.8	5.9	12	2.0
Cancer of esophagus (150)	13.1	57	4.4	5.4	6	1.1
Stomach and duodenal ulcers (540-1)	23.0	99	4.3	13.0	40	3.1
Other circulatory diseases (451-468)	99.0	227	2.3	45.8	93	2.0
Cirrhosis of liver (581)	57.3	85	1.5	22.4	27	1.2
Cancer of bladder (181)	58.2	73	1.3	29.8	31	1.0
Coronary artery disease (420)	2,335.0	3,262	1.4	1,245.0	1,731	1.4
Other heart diseases (421-2, 430-4)	225.9	321	1.4	124.1	178	1.4
Hypertensive heart disease (440-3)	144.4	174	1.2	93.0	133	1.4
General arteriosclerosis (450)	106.8	146	1.4	63.7	75	1.2
Cancer of kidney (180)	25.0	37	1.5	13.9	25	1.8
All other cancer	272.9	339	1.2	199.3	239	1.2
Cancer of stomach (151)	101.0	139	1.4	51.4	66	1.3
Influenza, pneumonia (480-493)	199.2	153	0.8	55.1	55	1.0
All other causes	769.3	790	1.0	308.1	357	1.2
Cerebral vascular lesions (330-4)	634.0	605	1.0	300.1	321	1.1
Cancer of prostate (177)	97.1	118	1.2	52.0	57	1.1
Accidents, suicides, violence (800-999)	287.1	316	1.1	169.6	159	0.9
Nephritis (592-4)	20.7	44	1.4	21.7	23	1.1
Rheumatic heart disease (400-416)	96.0	86	0.9	47.9	59	1.2
Cancer of rectum (154)	89.7	64	0.7	43.3	38	0.9
Cancer of intestines (152-53)	149.6	164	1.1	85.8	97	1.1
All causes	5,941.1	8,062	1.4	3,045.5	4,107	1.35

[1] British doctors, U.S. veterans and Canadian veterans.
[2] British doctors, men in nine States, U.S. veterans, and Canadian veterans.
[3] "Bronchitis and emphysema" includes "other bronchopulmonary diseases" for men in nine States and Canadian veterans.

parisons suggest by analogy that the differences in death rates from constitutional or genetic factors may be moderate or small rather than large.* Further, it seems unlikely that constitutional or genetic differences between cigar and pipe smokers and between these groups and non-smokers can have any substantial effect on their death rates, since the over-all death rates of these three groups differ only slightly.

Finally, part of the difference may represent a general debilitating effect of cigarette smoking in addition to marked effects on a few diseases. Pearl's hypothesis that smoking increases the "rate of living" is of this type, though there are difficulties in making this hypothesis precise enough to be subject to medical investigation. Hammond (13) has suggested that the explanation might lie in the effect of cigarette smoking in decreasing the quantity of oxygen per unit volume of blood, but there are numerous medical objections to this hypothesis. This Committee has no information that would lead it to favor one or another of the possible explanations put forward above.

*This question is discussed more fully in Chapter 9, p. 190.

Mortality Ratios for Cigarette Smokers by Amount Smoked

For coronary artery disease and lung cancer, the mortality ratios are given by amount smoked in Tables 21 and 22 for current smokers of cigarettes only.

In Table 21 an increasing trend with amount smoked appears in all five studies. The two California studies, in which the data are for all cigarette smokers (current and ex-smokers combined) show a less marked trend.

Table 21.—*Mortality ratios for coronary artery disease for smokers of cigarettes only by amount smoked*

Number of packs per day	British doctors	Men in 9 States	U.S. veterans	Canadian veterans	Men in 25 States
<½	1.0	1.2	1.3	1.7	1.3
½–1	1.5	1.9	1.8	1.7	2.0
1–2	[1] 1.7	2.1	1.7	[1] 2.0	2.1
Over 2	.....	2.4	1.9	.....	2.5

[1] More than one pack.

Table 22.—*Lung cancer mortality ratios for current smokers of cigarettes only by amount smoked*

Number of packs per day	British doctors	Men in 9 States	U.S. veterans	Canadian veterans
<½	4.4	5.8	5.2	8.4
½–1	10.8	7.3	9.4	13.5
1–2	[1] 43.7	15.9	18.1	[1] 15.1
Over 2	.....	21.7	23.3	.....

[1] Over one pack.

The trends in lung cancer mortality ratio with amount smoked are steep in all four studies. The two California studies also show marked trends for all cigarette smokers combined.

For the six causes of death (other than lung cancer) that were pointed out in Table 19 as having unusually high mortality ratios, the numbers of deaths permit a breakdown only into two amounts smoked. The results from six studies are shown in Table 23. Data were not available from the

Table 23.—*Expected and observed deaths and mortality ratios for current cigarette smokers, for selected causes of death, by amount smoked, in six studies*

Causes of death	One pack or less			More than one pack		
	Number of deaths		Mortality ratio	Number of deaths		Mortality ratio
	Expected	Observed		Expected	Observed	
Bronchitis and emphysema	44.6	225	5.0	17.2	147	8.5
Cancer of larynx	3.6	19	5.3	4.1	31	7.5
Cancer of oral cavity	16.8	53	3.2	14.8	60	4.1
Cancer of esophagus	13.2	40	3.0	9.7	48	4.9
Stomach and duodenal ulcers	32.5	110	3.4	31.2	91	2.9
Other circulatory	98.5	253	2.6	60.4	175	2.9
Cancer of the bladder	57.3	80	1.4	23.7	73	3.1

men in the 25-State study. Cancer of the bladder is included in Table 23 as background data for Chapter 9.

All causes except stomach and duodenal ulcers show some increase in the mortality ratio for the heavier smokers. The rate of increase cannot be regarded as accurately determined in view of the small numbers of deaths.

Cigars and Pipes

In view of the small numbers of deaths involved, the data for cigar and pipe smokers were combined in Table 24, which lists the total expected deaths, total observed deaths and mortality ratios from five studies (British doctors, U.S. Veterans, Canadian Veterans, and men in 9 and 25 States). Causes of death with relatively high mortality ratios are oral cancer (3.4), cancer of the esophagus (3.2), cancer of the larynx (2.8), cancer of the lung (1.7), cirrhosis of the liver (1.6), and stomach and duodenal ulcers (1.6). It should be noted that all these ratios are based on modest numbers of deaths.

Table 24.—*Numbers of expected and observed deaths and mortality ratios for cigar and pipe smokers, in five studies* [1]

Underlying cause of death	Number of deaths		Mortality ratio
	Expected	Observed	
Cancer of oral cavity (140–5)	13.5	46	3.4
Cancer of esophagus (150)	10.2	33	3.2
Cancer of larynx (161)	3.2	9	2.8
Cancer of lung (162–3)	65.2	113	1.7
Cirrhosis of liver (581)	47.5	77	1.6
Stomach and duodenal ulcers (540–1)	35.2	56	1.6
Cancer of kidney (180)	30.8	39	1.3
Cancer of intestines (152–3)	174.6	219	1.3
Other circulatory diseases (451–468)	89.1	105	1.2
All other cancer	396.7	456	1.1
Cancer of prostate (177)	127.2	144	1.1
Cancer of stomach (151)	116.8	132	1.1
Cancer of rectum (154)	78.2	88	1.1
Hypertensive heart disease (440–3)	194.5	218	1.1
Other heart diseases (421–2, 430–4)	272.6	303	1.1
Bronchitis and emphysema (502, 527.1)	33.7	37	1.1
Cerebral vascular lesions (330–4)	685.3	720	1.1
Coronary artery disease (420)	2,721.5	2,842	1.0
All other causes	612.9	587	1.0
Influenza and pneumonia (480–493)	93.8	88	0.9
Accidents, suicides, violence (800–999)	347.1	318	0.9
Cancer of bladder (181)	63.1	56	0.9
General arteriosclerosis (450)	124.1	109	0.9
Nephritis (592–4)	63.6	55	0.9
Rheumatic heart disease (400–416)	100.5	69	0.7
All causes	6,500.9	6,919	1.06

[1] Includes British doctors, men in 9 States, U.S. veterans, Canadian veterans, and men in 25 States; includes ex-smokers for men in 9 States; excludes pipe smokers for Canadian veterans.

Separate breakdowns by cause of death for cigar-only smokers and for pipe-only smokers are available in only three studies. The numbers of deaths are too few to throw any light on the question whether there are differences between cigar and pipe smokers in the causes of death for which mortality ratios are elevated.

Several of the reports previously published on these studies have included a table showing how the excess number of deaths of cigarette smokers over non-smokers is distributed among the principal causes of death. For each cause, the difference between the observed and the expected number of deaths for cigarette smokers is divided by the total excess for all causes, and multiplied by 100 to express the figures on a percentage basis. Table 25 presents these percentages for the seven studies for 13 groups of causes. A negative percentage, which occurs in a few places in the table, implies that for this cause the observed smoker deaths were smaller than the expected deaths.

TABLE 25.—*Percentage of total number of excess deaths of cigarette smokers due to different causes* [1]

Underlying cause	British doctors	Men in 9 States	U.S. veterans	California occupational	California Legion	Canadian veterans	Men in 25 States
Coronary artery disease	32.9	31.9	38.6	43.5	43.5	44.2	31.7
Other heart disease	9.8	2.1	6.8	1.4	4.5	5.9	5.5
Cerebral vascular lesions	6.1	4.5	4.9	5.3	6.5	−1.8	3.3
Other circulatory diseases	1.9	2.7	7.1	1.7	0.2	5.6	4.4
Cancer of lung	24.0	13.5	14.9	20.2	16.8	13.3	13.6
Cancer of oral cavity, esophagus, larynx	3.3	2.9	2.7	0.3	3.0	2.2	2.2
Other cancer	−0.3	9.8	8.9	6.3	−2.2	7.2	7.6
Bronchitis and emphysema	9.6	1.1	4.0	1.3	5.6	8.2	3.8
Influenza and pneumonia	−2.4	1.6	0.4	2.4	1.8	1.5	1.5
Stomach and duodenal ulcers	2.7	2.1	1.4	−1.7	2.2	2.9	1.2
Cirrhosis of liver	2.9	1.6	2.5	6.9	2.3	0.8	0.9
Accidents, suicides, violence	0.2	1.2	2.0	3.3	2.7	4.6	0.8
All other causes	9.2	3.0	5.8	4.2	12.5	0.4	2.4
All causes	100.0	100.0	100.0	100.0	100.0	100.0	100.0

[1] All cigarette smokers (current and ex-) for the two California and men in 25 States studies; current cigarette smokers only for the remainder.

As previous writers have noted, all studies agree in showing coronary artery disease as the prime contributor to excess mortality, with lung cancer in second place. Other rubrics that show a substantial contribution in some studies, though not in all, are bronchitis and emphysema, cancers other than those of the mouth and lungs, and heart disease other than coronary.

SUMMARY

This report summarizes the results of the seven major prospective studies of the relative death rates of male smokers and non-smokers.

TOTAL MORTALITY

Cigarette Smokers

The death rate for smokers of cigarettes only who were smoking at the time of entry is about 70 percent higher than that for non-smokers.

TABLE 26.—*Numbers of expected and observed deaths for smokers of cigarettes only, and mortality ratios, each prospective study and all studies*

Cause of death	British doctors			Men in 9 States			U.S. veterans			California occupational		
	Deaths		Mortality ratio	Deaths		Mortality ratio	Deaths		Mortality ratio	Deaths		Mortality ratio
	Expected	Observed		Expected	Observed		Expected	Observed		Expected	Observed	
Cancer of lung (162-3)	6.4	129	20.2	23.4	233	10.0	43.3	519	12.0	8.7	128	15.9
Bronchitis, emphysema (502, 527.1)	4.2	52	12.5	12.8	30	2.3	14.4	141	9.8	2.6	11	4.3
Cancer of larynx (161)	.0	7	----------	1.3	17	13.1	2.4	14	5.8	.0	3	----------
Cancer of oral cavity (140-6)	.0	6	----------	7.8	22	2.8	8.1	54	6.6	7.2	7	1.0
Cancer of esophagus (150)	3.2	7	2.1	2.7	18	6.6	5.2	33	6.4	5.5	4	.7
Stomach and duodenal ulcers (540, 541)	.0	14	----------	12.2	61	5.0	21.5	67	3.1	23.1	12	.5
Other circulatory diseases (451-68)	17.2	27	1.6	19.7	53	2.7	66.4	228	3.4	11.5	18	1.6
Cirrhosis of liver (581)	.0	15	----------	23.5	49	2.1	31.2	111	3.6	14.7	59	4.0
Cancer of bladder (181)	13.9	12	.9	17.2	41	2.4	31.4	55	1.8	2.2	13	6.0
Coronary artery disease (420)	268.9	525	1.5	927.7	1,734	1.9	1,903.3	3,037	1.7	273.9	551	2.0
Other heart disease (423-2, 430-4)	78.8	115	1.5	72.5	108	1.5	122.2	244	2.0	23.8	24	1.0
Hypertensive heart disease (440-3)	21.0	32	1.5	88.7	107	1.2	138.7	223	1.6	27.2	28	1.0
General arteriosclerosis (450)	21.2	21	1.0	9.1	18	2.0	97.0	163	1.7	.0	5	----------
Cancer of kidney (189)	.0	8	----------	14.0	21	1.5	23.1	34	1.5	.0	10	----------
All other cancer	81.7	73	.9	132.9	230	1.7	315.8	457	1.4	72.1	105	1.5
Cancer of stomach (151)	28.3	31	1.1	33.7	76	2.3	61.5	90	1.5	31.4	24	.8
Influenza, pneumonia (480-96)	47.0	35	.7	15.6	41	2.6	22.6	36	1.6	10.3	25	2.4
All other causes	144.0	182	1.3	209.5	263	1.3	354.8	530	1.5	68.9	101	1.5
Cerebral vascular lesions (290-4)	161.1	192	1.2	228.8	279	1.3	309.1	467	1.5	42.2	76	1.8
Cancer of prostate ([illegible])	28.0	15	.5	32.4	51	1.6	53.7	106	2.0	8.6	4	.5
Accidents, suicides, violence (800-99)	89.2	90	1.0	174.1	192	1.1	241.5	306	1.3	108.4	161	1.5
Nephritis (592-4)	8.1	17	2.1	43.3	34	.8	18.6	30	1.6	16.0	10	.6
Rheumatic heart disease (400-16)	10.2	13	1.3	48.4	43	.9	67.4	77	1.1	22.9	31	1.4
Cancer of rectum (154)	4.2	15	3.6	29.8	25	.8	68.7	62	.9	13.6	14	1.0
Cancer of intestines (152-3)	28.1	28	1.1	65.6	35	.5	121.2	152	1.3	23.7	22	.9
All causes	1,161.8	1,672	1.44	2,227.7	3,781	1.70	4,043.1	7,236	1.79	818.5	1,456	1.78

TABLE 26.—*Numbers of expected and observed deaths for smokers of cigarettes only, and mortality ratios, each prospective study and all studies*—Continued

Cause of death	California Legion			Canadian veterans			Men in 25 States			Total, all studies			Median mortality ratio
	Deaths		Mortality ratio	Deaths		Mortality ratio	Deaths		Mortality ratio	Deaths		Mortality ratio	
	Expected	Observed		Expected	Observed		Expected	Observed		Expected	Observed		
Cancer of lung (162-3)	19.9	98	4.9	27.1	317	11.7	41.5	399	9.6	170.3	1,833	10.8	11.7
Bronchitis, emphysema (502, 527.1)	3.6	20	5.4	26.5	166	4.6	15.4	115	7.5	89.5	546	6.1	7.5
Cancer of larynx (161)	4.0	6	1.5	.0	5	----	6.3	23	3.7	14.0	75	5.4	5.8
Cancer of oral cavity (140-5)	5.7	10	1.9	5.1	20	3.9	3.6	33	9.2	37.0	152	4.1	3.9
Cancer of esophagus (150)	1.8	9	5.1	6.8	22	3.3	8.4	20	2.4	33.7	113	3.4	3.3
Stomach and duodenal ulcers (540, 541)	1.8	12	6.8	7.9	54	6.9	38.6	74	1.9	105.1	294	2.8	5.0
Other circulatory diseases (451-68)	16.7	37	2.2	41.5	96	2.3	81.0	190	2.5	254.0	649	2.6	2.3
Cirrhosis of liver (581)	13.1	23	1.8	37.6	50	1.3	49.1	72	1.5	169.2	379	2.2	2.1
Cancer of bladder (181)	1.8	7	4.0	22.3	38	1.7	22.8	50	2.2	111.6	216	1.9	2.2
Coronary artery disease (420)	312.8	515	1.7	982.5	1,982	1.8	1,863.6	3,223	1.7	6,430.7	11,177	1.7	1.7
Other heart diseases (421-2, 430-4)	12.1	26	2.0	75.3	156	2.1	140.3	195	1.4	526.0	868	1.7	1.5
Hypertensive heart disease (440-3)	24.9	29	1.2	36.2	58	1.6	71.5	154	2.2	409.2	631	1.5	1.5
General arteriosclerosis (450)	20.1	20	.5	14.7	48	3.3	29.6	35	1.2	210.7	310	1.5	1.7
Cancer of kidney (180)	8.3	6	.7	9.5	13	1.4	24.1	28	1.2	79.0	120	1.5	1.4
All other cancer	75.4	84	1.1	104.1	149	1.4	279.4	426	1.5	1,061.4	1,524	1.4	1.4
Cancer of stomach (151)	20.5	25	1.2	41.2	76	1.9	68.6	91	1.3	285.2	413	1.4	1.3
Influenza, pneumonia (480-96)	14.7	22	1.5	135.0	159	1.2	58.0	97	1.7	303.2	415	1.4	1.6
All other causes	99.1	94	2.4	361.5	360	1.0	330.9	416	1.3	1,508.7	1,946	1.3	1.3
Cerebral vascular lesions (330-4)	87.1	87	1.5	294.1	255	.9	389.4	477	1.2	1,461.8	1,844	1.3	1.3
Cancer of prostate (177)	22.1	19	.9	32.3	48	1.5	74.9	75	1.0	253.0	318	1.3	1.0
Accidents, suicides, violence (800-999)	45.0	62	1.4	101.3	174	1.7	303.7	325	1.1	1,063.2	1,310	1.2	1.3
Nephritis (592-4)	.0	3	----	11.6	17	1.5	58.8	62	1.1	156.4	173	1.1	1.5
Rheumatic heart disease (400-16)	14.2	18	1.3	48.1	39	.8	79.4	88	1.1	290.6	309	1.1	1.1
Cancer of rectum (154)	12.0	9	.8	41.3	24	.6	39.2	64	1.7	207.8	213	1.0	.9
Cancer of intestines (152-3)	23.2	13	.4	46.6	64	1.4	106.2	81	.8	422.6	395	.9	.9
All causes	799.4	1,264	1.58	2,420.1	4,001	1.65	4,183.3	6,813	1.63	15,653.9	26,223	1.68	1.65

The death rates increase with the amount smoked. For groups of men smoking less than 10, 10–19, 20–39, and 40 cigarettes and over per day, respectively, the death rates are about 40 percent, 70 percent, 90 percent and 120 percent higher than for non-smokers.

The ratio of the death rates of smokers to that of non-smokers is highest at the earlier ages (40–50) represented in these studies, and declines with increasing age. The same effect appears to hold for the ratio of the death rate of heavy smokers to that of light smokers.

In the studies that provided this information, the mortality ratio was substantially higher for men who started to smoke under age 20 than for men who started after age 25. In general, the mortality ratio was increased as the number of years of smoking increased, although the pattern of increase was irregular from study to study.

In two studies which recorded the degree of inhalation, the mortality ratio for a given amount of smoking was greater for inhalers than for non-inhalers.

Cigarette smokers who had stopped smoking prior to enrollment in the study had mortality ratios about 1.4 as against 1.7 for current cigarette smokers. Two studies reported the number of years since smoking was stopped. In these, the mortality ratio declined in general as the number of years of cessation increased. The mortality ratio of ex-cigarette smokers increased with the number of years of smoking and was higher for those who stopped after age 55 than for those who stopped at an earlier age. (These results were available in one study only.)

Taken as a whole the seven studies offer a substantial breadth of sampling of the type of men and environmental exposures to be found in North America and Britain, although none of the groups studied was planned as a random sample of the U.S. male population. All the studies had death rates below those of the U.S. white male population in 1960. To some extent this is to be expected, since men in poor health were likely to be under-recruited in these studies. Only a minor part of these differences in death rates can be attributed to a failure to trace all deaths or to higher death rates among non-respondents in these studies.

The data on smoking status and on amount smoked were subject to errors of measurement, particularly since smoking status was measured only once and some men presumably changed their status after entry into the study. For men designated as current smokers of cigarettes only, our judgment is that the net effect of such errors of measurement is to make the observed mortality ratios relative to non-smokers underestimates of the true mortality ratios.

The studies suffered from a failure to obtain substantial portions of the study populations selected for investigation. For a non-response rate of 32 percent in the prospective studies, calculations based on the available information about the non-respondents indicate that reported mortality ratios lying between 1 and 2 might overestimate the corresponding figure for the complete study population by 0.2 or 0.3. In our judgment these biases can account for only a part of the elevation in mortality ratios found for cigarette smokers (see Appendix 1).

In three studies in which the data could be subdivided by size of city, the mortality ratios differed little in the four sizes of communities studied.

In one study numerous other variables that might influence the death rate, such as longevity of parents and grandparents, use of alcohol, occupational exposure and educational level, were recorded. Adjustment for each of these variables individually produced little change in the mortality ratios.

Although similar information from other studies would have been welcome, it is our judgment that the mortality ratios are unlikely to be explained by such environmental, social class, or ethnic differences between cigarette smokers and non-smokers.

Except for the analyses reported above by longevity of parents and grandparents and by previous serious disease, no direct information is available on whether there are basic constitutional differences between cigarette smokers and non-smokers that would affect their longevity. As described elsewhere in this report, differences have been found between cigarette smokers and non-smokers on certain psychological and behavioral variables. However, even for these variables the distributions for cigarette smokers and non-smokers show considerable overlap. It seems a reasonable opinion that the same situation would apply to the constitutional hardiness of cigarette smokers and non-smokers, if it were possible to measure such a variable. This implies that constitutional differences, if they exist, are likely to express themselves in only a moderate difference in death rates.

Cigar Smokers

Death rates are about the same as those of non-smokers for men smoking less than five cigars daily. For men smoking five or more cigars daily, death rates were slightly higher (9 percent to 27 percent) than for non-smokers in the four studies that gave this information. There is some indication that this higher death rate occurs primarily in men who have been smoking for more than 30 years and in men who stated they inhaled the smoke to some degree.

Death rates for ex-cigar smokers were higher than those for current smokers in all four studies in which this comparison could be made.

Pipe Smokers

Death rates for current pipe smokers were little if at all higher than for non-smokers, even with men smoking 10 or more pipefuls per day and with men who had smoked pipes for more than 30 years.

Ex-pipe smokers, on the other hand, showed higher death rates than both non-smokers and current smokers in four out of five studies. The epidemiological studies on ex-cigar and ex-pipe smokers are inadequate to explain this puzzling phenomenon. According to Hammond and Horn (10) and Dorn (6) the explanation may be that a substantial number of cigar and pipe smokers stop smoking because of illness.

Mortality by Cause of Death

In the combined results from these seven studies, the mortality ratio of cigarette smokers was particularly high for a number of diseases: cancer of

the lung (10.8), bronchitis and emphysema (6.1), cancer of the larynx (5.4), oral cancer (4.1), cancer of the esophagus (3.4), stomach and duodenal ulcers (2.8), and the rubric, 451–468, "other circulatory diseases" (2.6). For coronary artery disease, the mortality ratio was 1.7.

There is a further group of diseases, including some of the most important chronic diseases, for which the mortality ratio for cigarette smokers lay between 1.2 and 2. The explanation of the moderate elevations in mortality ratios in this large group of causes is not clear. Part may be due to the sources of bias previously mentioned or to some constitutional and genetic difference between cigarette smokers and non-smokers. There is the possibility that cigarette smoking has some general debilitating effect, although no medical evidence that clearly supports this hypothesis can be cited. The substantial number of possibly injurious agents in tobacco and its smoke also may explain the wide diversity in diseases associated with smoking.

In all seven studies, coronary artery disease is the chief contributor to the excess number of deaths of cigarette smokers over non-smokers, with lung cancer uniformly in second place.

For cigar and pipe smokers combined, the data suggest relatively high mortality ratios for cancers of the mouth, esophagus, larynx and lung, and for cirrhosis of the liver and stomach and duodenal ulcers. These ratios are, however, based on small numbers of deaths.

APPENDIX I

Appraisal of Possible Biases Due to Non-response

The non-response rates in the prospective studies were approximately as follows: 15 percent for the California occupational study; 15 percent for the U.S. veterans' study during the 3-year period 1957–1959 and 32 percent during the 3-year period 1954–1956; 32 percent for the British doctors' study; and about 44 percent for the California Legion study and the Canadian veterans' study. In forming a judgment about the size of the bias that may be due to non-response, we have concentrated on a non-response rate of 32 percent, since this represents roughly an average figure for these five studies. The objective is to estimate by how much the mortality ratio for the whole population might differ from that found in the respondents.

The only useful information in any detail about the non-respondents comes from the U.S. veterans' study. Table 27 shows data on death rates in 1958 and 1959 (16).

For the present purpose the 1957 respondents will be regarded as a part of the 32 percent of non-respondents to the original questionnaire for whom we are fortunate to have some data.

Table 27 indicates that the non-respondents in 1954 have higher death rates than respondents for both non-smokers and smokers. For non-smokers the ratio of the death rate of 1957 respondents to 1954 respondents was 1.35 in

TABLE 27.—*Age-adjusted death rates (per 1,000 person-years) for 1954 respondents, 1957 respondents, and non-respondents in U.S. veterans study*

Groups		Proportion in population	Death rates	
			1958	1959
1954 respondents	Non-smokers	0.17	13.29	12.84
	All smokers	.61	19.26	19.00
1957 respondents	Non-smokers	.04	17.96	16.87
	All smokers	.13	22.67	21.61
Non-respondents	All	.18	21.99	19.84

1958 and 1.27 in 1959. For smokers the corresponding figures are 1.18 in 1958 and 1.14 in 1959.

If the adjusted death rates in Table 27 are weighted by the proportions of men in the population, it is found that the over-all 1958 death rate for 1954 respondents was 17.77 as compared with 19.05 for the complete study population. The ratio 19.05/17.77 is 1.07, so that in 1958 the death rate for the study population was 7 percent higher than for the 1954 respondents. In 1959 the corresponding death rates were 17.46 for 1954 respondents and 18.31 for the complete population, the ratio being 1.05. These ratios agree with Doll's judgment (4) that in the British doctors' study the death rate in the complete population may exceed that in his 68 percent of respondents by from 5 percent to 10 percent.

Comparison of the 1954 and 1957 respondents also suggests that the non-respondents in 1954 contain a higher proportion of smokers than the respondents. In the 1954 respondents, non-smokers contributed 183,094 person-years of experience during 1957–1959 as compared with 179,750 person-years for current smokers of cigarettes only, non-smokers representing 50.6 percent of the total of the two groups. Among the 1957 respondents the corresponding figure was 46.8 percent. A further decline may have occurred in the non-respondents to the 1957 questionnaire.

From these data the following assumptions were made in investigating the non-response bias as it affects the mortality ratio of current smokers of cigarettes only.

1. The proportions of the relevant groups in the complete population are as follows:

Groups	Non-smokers	Cigarette smokers	Total
Non-respondents	0.14	0.18	0.32
Respondents	.34	.34	.68
Complete population	.48	.52	1.00

This assumes that in the 68 percent of respondents, non-smokers constitute 50 percent of non-smokers plus cigarette smokers, but in the non-respondents this figure has dropped to 44 percent.

2. The death rate in the complete population is 10 percent higher than in the respondents.

3. One further numerical relationship is needed in order to obtain concrete results. For this, the computations were made under two different sets of assumptions. The more extreme (3a) is that cigarette smokers have no higher death rates among non-respondents than among respondents. The alternative (3b) is that the death rate of cigarette smokers was 10 percent higher among non-respondents than among respondents. Both sets of assumptions seem more extreme than the indications from the U.S. veterans' study in which, as already noted, the smoker death rates were 18 percent and 14 percent higher among 1957 respondents than among 1954 respondents.

For total mortality, the calculations of most interest are those for a mortality ratio of 1.7 among the respondents, since this is the average ratio found in the prospective studies for smokers of cigarettes only. For individual causes of death, however, the mortality ratios among respondents range from 1 to 10, so that calculations were made for a series of different mortality ratios among respondents. Table 28 illustrates the calculations made on assumptions (3a) and (3b) for a mortality ratio of 1.7 among respondents.

TABLE 28.—*Illustration of calculation of non-response bias*

Assumption (3a)

	Mortality ratios		
	Non-smokers	Cigarette smokers	
Non-respondents.....	[6] (1.865)	1.700	[5] (1.772)
Respondents.....	1.000	1.700	[4] (1.350)
Complete population.	[1] (1.252)	[2] (1.700)	[3] (1.455)
M.R.....	[7] (1.36)		

Assumption (3b)

	Mortality ratios		
	Non-smokers	Cigarette smokers	
Non-respondents.....	[6] (1.646)	1.870	[5] (1.737)
Respondents.....	1.700	1.700	[4] (1.350)
Complete population.	[1] (1.188)	[2] (1.786)	[3] (1.455)
M.R.....	[7] (1.48)		

The figures without parentheses in the mortality ratio tables represent the start of the computations. The indexes ([1], etc.) show the order in which other figures are computed. For assumption (3a):

(1.350) [4] = [(0.34)(1.000) + (0.34)(1.700)]/(0.68)
(1.455) [3] = (1.1)(1.350)
(1.772) [5] = [(1.455) − (0.68)(1.350)]/(0.32)
(1.865) [6] = [(0.32)(1.772) − (0.18)(1.700)]/(0.14)
(1.252) [1] = [(0.14)(1.865) + (0.34)(1.000)]/(0.48)
(1.700) [2] = [(0.18)(1.700) + (0.34)(1.700)]/(0.52)
(1.36) [7] = 1.700/1.252

Thus, the mortality ratio drops from 1.7 to 1.36 in the complete population under assumption (3a) and to 1.48 under assumption (3b). One consequence of assumption (3a) is that the mortality ratio of cigarette smokers among the non-respondents is less than 1.

Table 29 shows the results obtained for a range of mortality ratios in the respondent population.

For the high mortality ratios the assumptions may appear unduly extreme. For instance, under assumption (3a) with mortality ratio 10.0 in the respondents, the non-smoker death rate in the non-respondents has to be 3.6 times

that in the respondents, although the smoker death rates are assumed the same in respondents and non-respondents.

It may be of interest to quote Berkson's (1) example in the same form (Table 30).

TABLE 29.—*Mortality ratios in respondents and computed values for the complete population*

In respondents (68 percent)	In complete population	
	Assumption (3a)	Assumption (3b)
1.2	1.00	1.06
1.4	1.14	1.23
1.6	1.28	1.40
1.8	1.43	1.56
2.0	1.57	1.73
5.0	3.43	4.07
10.0	5.85	7.41

TABLE 30.—*Proportions and death rates for Berkson's example*

Group	Proportions			Death rates		Total
	Non-smokers	Smokers	Total	Non-smokers	Smokers	
Non-respondents	0.00494	0.28360	0.28854	60.121	4.217	5.174
Respondents	.19506	.51640	.71146	1.553	2.339	2.118
Total	.20000	.80000	1.00000	3.000	3.000	3.000

In their general direction, Berkson's assumptions are similar to those made in this Appendix, but the differences in death rates between respondents and non-respondents were more extreme in his example. The death rate in the complete population (3.000) was 42 percent higher than the respondent death rate. The non-smoker death rate was over 38 times as high among non-respondents as among respondents (60.121/1.553), whereas among the smokers it was only 1.8 times as high. His calculations referred to the early years of a study, in which the effects of differential entry of ill persons among smokers and non-smokers are likely to be most marked. Further, as we interpret his writing, the example was intended as a warning against the type of subtle bias that can arise whenever a study has a high proportion of non-respondents, rather than a claim that this numerical estimate of the bias actually applied to these studies.

To summarize, the amounts of non-response in the prospective studies could have produced sizable biases in the estimated mortality ratios. Taking assumption 3b in Table 29, as representing fairly extreme conditions, it appears that a reported mortality ratio between 1 and 2 might overestimate by 0.3, a ratio of 5.0 by 1.0 and a ratio of 10.0 by 3.0.

APPENDIX II

Stability of Mortality Ratios

In computing the mortality ratio of a group of smokers to a group of non-smokers, each group is subdivided into age-classes (usually 5-year). For the ith age-class let y_i denote the number of smoker deaths and x_i the number of non-smoker deaths. The "expected" number of smoker deaths in the ith class (expected on the assumption that smokers have the same age-specific death rates as non-smokers) is

$$\frac{\text{(Person-years for smokers in class i)}}{\text{(Person-years for non-smokers in class i)}} x_i = \lambda_i x_i \qquad \text{(say)}$$

The estimated mortality ratio $\hat{R}$ is defined as

$$\hat{R} = \frac{\Sigma y_i}{\Sigma \lambda_i x_i} \qquad (1)$$

summed over the age-classes.

In the interpretation of the values of R found in the seven studies, much weight has been given to the consistency of the values from one study to another, on the grounds that if the values of R for a particular cause of death are high in all seven studies, this evidence is more impressive than R values that are high in say, three studies but show no elevation in the remaining four studies. As a consequence, the question whether the value of $\hat{R}$ in an individual study is significantly above unity, in the technical sense of this term, becomes less important. Nevertheless, an answer to this question is occasionally useful in the analysis. Moreover, for some causes of death the total numbers of deaths, even when all seven studies are combined, are small enough so that a measure of the stability of the combined $\hat{R}$ is needed.

Assumptions

In attempting to get some idea of the stability of $\hat{R}$ without too much complexity, the following assumptions will be made.

1. The numbers of deaths y_i and x_i are distributed as Poisson variables. As Chiang (3) has shown, a more accurate assumption is to regard y_i and x_i as binomial numbers of successes. But with causes of death for which the probability of dying in a 5-year age span is very small the Poisson assumption, which is slightly conservative, is reasonable.

2. The quantities λ_i can be regarded as known constants. This is not quite correct. Initially, the λ_i are the ratios of the numbers of smokers to non-smokers in the age-classes, which can reasonably be regarded as given. In subsequent years, however, the numbers are depleted by deaths, and the number of deaths is a random variable. When death rates are small, however, this assumption should introduce little error.

3. The variates y_i and y_j are uncorrelated. An error in the age assigned to a death, putting it in the wrong age-class, induces a negative correlation between y_i and y_j. The existence of such errors should have no effect on

the variance ascribed to Σy_i on the assumption of independence. The same remarks apply to the assumption that x_i and x_j are uncorrelated.

4. The variates x_i and y_i are uncorrelated. An error in assigning a death to the correct smoking category would induce a negative correlation between x_i and y_i. Such errors should of course not be allowed to happen, since they vitiate the comparison of the death rates that is the main point of the study, but occasional errors of this type may have occurred.

With these assumptions the numerator Σy_i of $\hat{R}$ follows a Poisson distribution. The denominator $\Sigma \lambda_i x_i$ is a linear function of independent Poisson variates, and numerator and denominator are independent of one another. The exact distribution of a ratio of this type has not been worked out. Two approximate methods of obtaining confidence limits for the true mortality ratio $\hat{R}$ will be given. Confidence limits are presented rather than the standard error of $\hat{R}$ because the distribution of $\hat{R}$ is skew when the numbers of deaths are moderate or small, so that the standard error is harder to interpret.

The Binomial Approximation

If the λ_i can be regarded as approximately constant ($=\lambda$, say) then $\hat{R}$ becomes of the form $y/\lambda x$, where y and x are independent Poisson variates. Since λx then represents the expected number of deaths of the smokers, the quantity λ is estimated as the ratio of the expected number of smoker deaths to the number of non-smoker deaths.

By a well-known result it follows that $x/(y+x)$, the ratio of non-smoker deaths to smoker plus non-smoker deaths, is distributed as a binomial proportion with

n = number of trials $= y+x$
p = probability of success $= 1/(1+\lambda R)$

where R is the true mortality ratio. Confidence limits for R are found from those for p.

Example. For the study of men in 25 States, the figures for lung cancer for cigar and pipe smokers are as follows:

	Non-smokers	Smokers	
	Observed	Observed	Expected
Number of deaths	16(x)	15(y)	9.71(λx)

Hence, $\lambda = 9.71/16 = 0.607$ and the binomial ratio is $16/31 = 0.516$. Hald's (9) table of the 95 percent two-tailed confidence limits of the binomial distribution gives 0.331 and 0.698 as the confidence limits for p. Those for R are given by the relation

$$R = (1-p)/\lambda p$$

This yields 0.7 and 3.3 as the 95 percent limits for R. Since the lower limit, 0.7, is less than unity, the estimated $\hat{R}$, 1.5, is not significantly above unity.

Unfortunately the assumption that λ_i is constant is not true in these studies. For instance, in the study of men in 25 States λ_i has the value 3.85 for cigarette smokers aged 45–49 and declines steadily with increasing age to a value of 0.96 for men aged 75–79. For cigar and pipe smokers the fluctuation in γ_i with age is less drastic but is still noticeable.

The Normal Approximation

This approach avoids the assumption that the λ_i are constant, but makes other assumptions that are shaky with small numbers of deaths. If R is the true mortality ratio, the quantity

$$y - Re$$

where $e = \Sigma\lambda_i x_i$ is the expected number of smoker deaths, will follow a distribution that has mean zero. If μ_i, m_i denote the true means of y_i and x_i, respectively, the variance of $(y - Re)$ is

$$\Sigma(\mu_i + R^2\lambda_i^2 m_i)$$

The basis of this approximation is to regard the quantity

$$\frac{y - Re}{\sqrt{\Sigma(\mu_i + R^2\lambda_i^2 m_i)}} \qquad (2)$$

as normally distributed with zero mean, since y_i and x_i are regarded, as previously, as independent Poisson variates. The 95 percent confidence limits for R are then obtained, by a standard device, by setting the absolute value of this quantity equal to 1.96 and solving the resulting quadratic equation for R.

Since the μ_i and the m_i are unknown, a further approximation is to substitute y as an estimate of $\Sigma\mu_i$ and $\Sigma\lambda_i^2 x_i$ as an estimate of $\Sigma\lambda_i^2 m_i$.

Example. For the example previously discussed the data are as follows:

$$y = 15: e = 9.71: \Sigma\lambda_i^2 x_i = 6.059$$

On squaring (2), the quadratic equation becomes

$$(15 - 9.71R)^2 = 3.84(15 + 6.059R^2)$$

The roots are found to be 0.7 and 3.4, in good agreement with the limits 0.7 and 3.3 given by the binomial approximation. This agreement is better than will usually be found with small numbers of deaths.

The following are 4 comparisons of the confidence limits for cigarette smokers in the same study.

Cause of death	Number of deaths			Mortality ratio	95 percent limits	
	Non-smokers observed	Cigarette smokers			Binomial	Normal
		Observed	Expected			
Cancer of lung	16	399	41.29	9.7	(5.0, 14.5)	(5.0, 21.4)
Emphysema	7	115	15.31	7.5	(3.3, 14.1)	(4.0, 40.0)
Cancer of rectum	18	64	58.42	1.7	(1.0, 3.3)	(1.0, 3.6)
Influenza and pneumonia	29	97	58.01	1.7	(1.1, 2.6)	(1.1, 2.9)

The lower confidence limits agree well, but the upper limit runs higher for the normal approximation. For cigarette smokers the normal method is perhaps more accurate. The binomial method has some advantage in simplicity.

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Chapter 9

Cancer

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CANCER MORBIDITY AND MORTALITY

Cancer has been the second ranking cause of death in the United States since 1937. Reviewing the mortality statistics of those parts of the United States which began relatively accurate reporting in 1900, (District of Columbia and 10 states—the so-called Death Registration Area of 1900) it can be seen that the number of cancer deaths per year has increased markedly (Figure 1). After subtracting the part of the increase due to growth of the population and the part due to increase in life expectancy or aging of the population, there is still a residual increase of significant proportions. While a part of this is undoubtedly due to improvement in diagnosis, most observers agree that a true increase in the cancer death rate has occurred during this time.

As general background information, it is useful to review the pattern of cancer risks found in the population of the United States as compared with the patterns in other countries. Segi has prepared systematic international compilations of cancer mortality (317). These show that the United States occupies an intermediate position in comparisons of death rates for all sites combined: the age-adjusted rates for U.S. males and females are lower than those in Austria and higher than in Norway and Japan (Figure 2). The point to be stressed, however, is not the rank order of countries according to over-all cancer mortality, but the differences in ranking for individual sites (Figures 3A and 3B). Mortality statistics, cancer register data, and collected series of pathological specimens are in general agreement in identifying individual countries as having their own characteristic site patterns of risk (146). Some of the more striking features in the United States are very low risks for esophagus and stomach and moderately high rates for urinary bladder; lung cancer mortality for males, while below the rates in England and Finland, is well above those in Canada, Norway and Japan.

Sources of Information

Information on morbidity and mortality from cancer in the United States comes from three principal sources: mortality statistics prepared by the National Vital Statistics Division of the U.S. Public Health Service, the large central registries receiving reports on diagnosed cases in Connecticut (136) upstate New York (112) and California (37), and the morbidity surveys conducted in ten metropolitan areas in 1937–39 and 1947–48 (91) and in Iowa in 1950 (148). Each body of material has its virtues and weaknesses. Mortality statistics report on the national experience and cover longer time spans than the specialized sources, but the diagnostic information in the death certifications is less reliable and complete. Recent studies of medical certifications have demonstrated that the quality of information for most

MORTALITY FROM CANCER (All sites), U.S. DEATH REGISTRATION AREA [1] OF 1900, 1900-1960

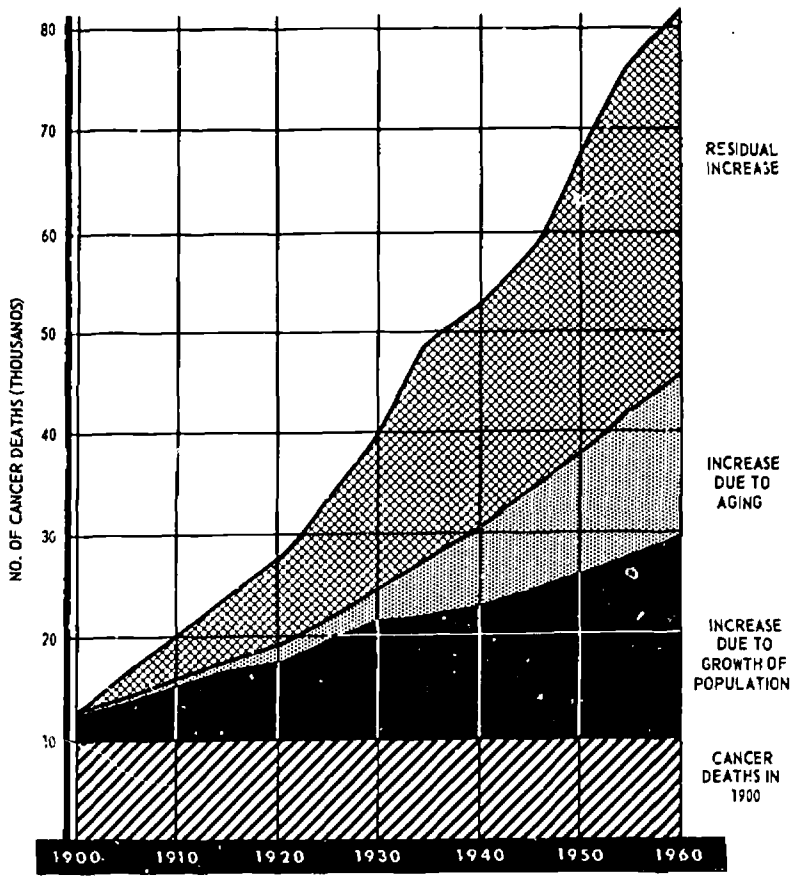


FIGURE 1.

Includes Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, Michigan, Indiana, District of Columbia.

Sources: a. United States Census of Population: 1940, 1950, 1960.
b. Vital Statistics of the United States, Part I, 1940; Vol. III, 1950; Vol. II, Part B, 1960.
c. Gover, Mary. Cancer Mortality in the United States, Part I, Public Health Bulletin 248, 1939.

cancer sites can be regarded as good (91, 247), so that the problems in interpretation are less formidable than those arising in studies of cardiovascular disease.

Completeness of reporting to the major registries is satisfactory and the accuracy of diagnostic information is excellent, but the registers cover only a limited number of areas. Fortunately, the registers in Connecticut

AGE-ADJUSTED MORTALITY RATES FOR CANCER - ALL SITES, IN 17 COUNTRIES 1958-1959.[1]

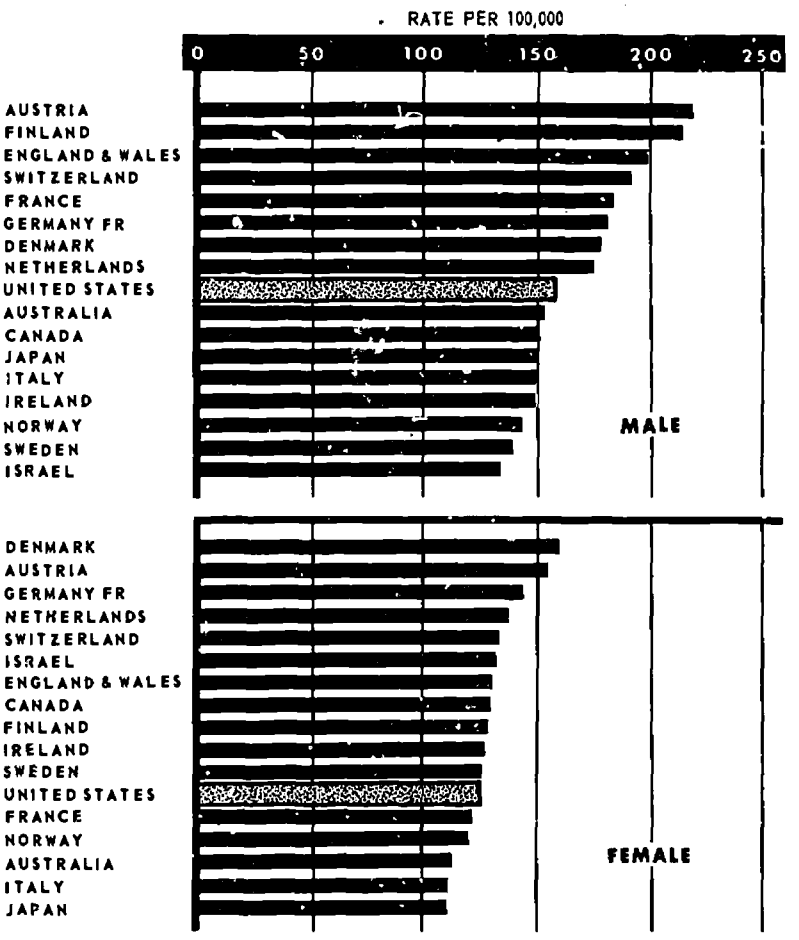


FIGURE 2.

U.S. data age-adjusted to total population of the continental United States, 1950.
Source: Calculated from Segi, M., and Kurihara, M. (317).

and New York have been in operation long enough to provide reliable data on incidence trends over the past two decades. The morbidity surveys for 1947–48 produced a comprehensive report on cancer incidence in large cities with very good medical care facilities, but this information has not been updated by resurveys.

AGE-ADJUSTED MORTALITY RATES FOR CANCER OF 6 SITES IN 6 SELECTED COUNTRIES - MALES [1]

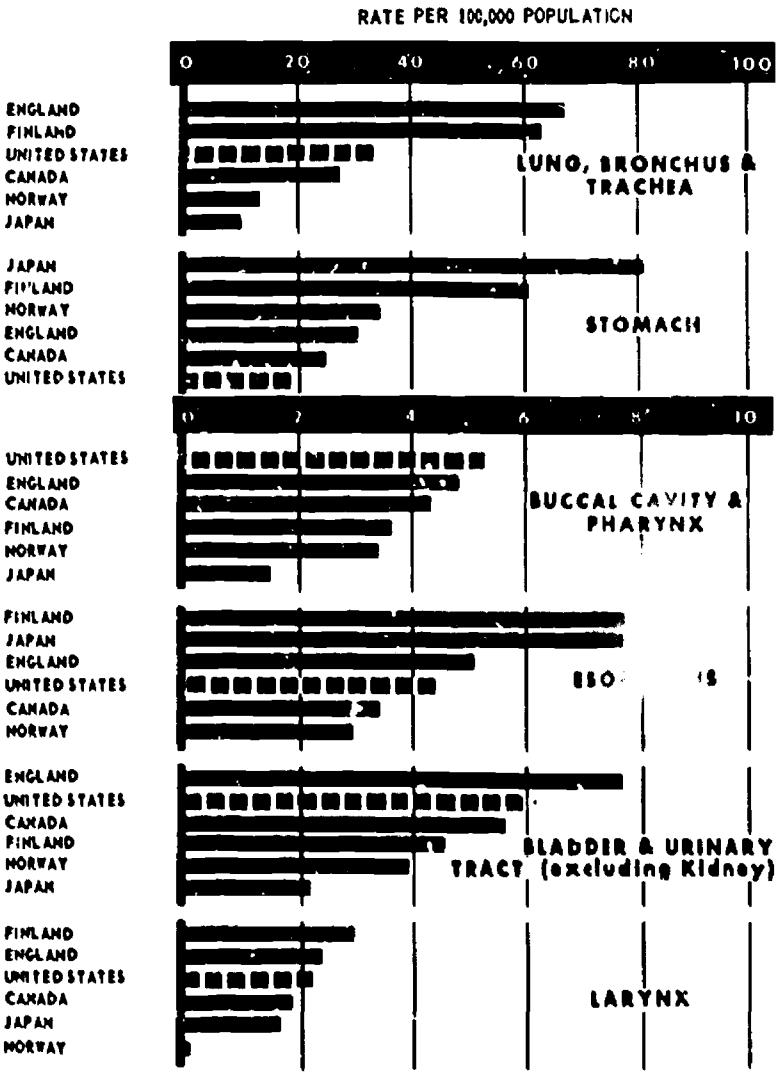


FIGURE 3A.

U.S. data age-adjusted to the total population of the continental United States, 1950.
Source: Calculated from Segi, M., and Kuribara, M. (317).

The deficiencies in any single set of data should not be overstressed. Comparisons of the various sources indicate good internal consistency among them and they usually lead to the same inferences on patterns of risk for

AGE-ADJUSTED MORTALITY RATES FOR CANCER OF 6 SITES IN 6 SELECTED COUNTRIES - FEMALES[1]

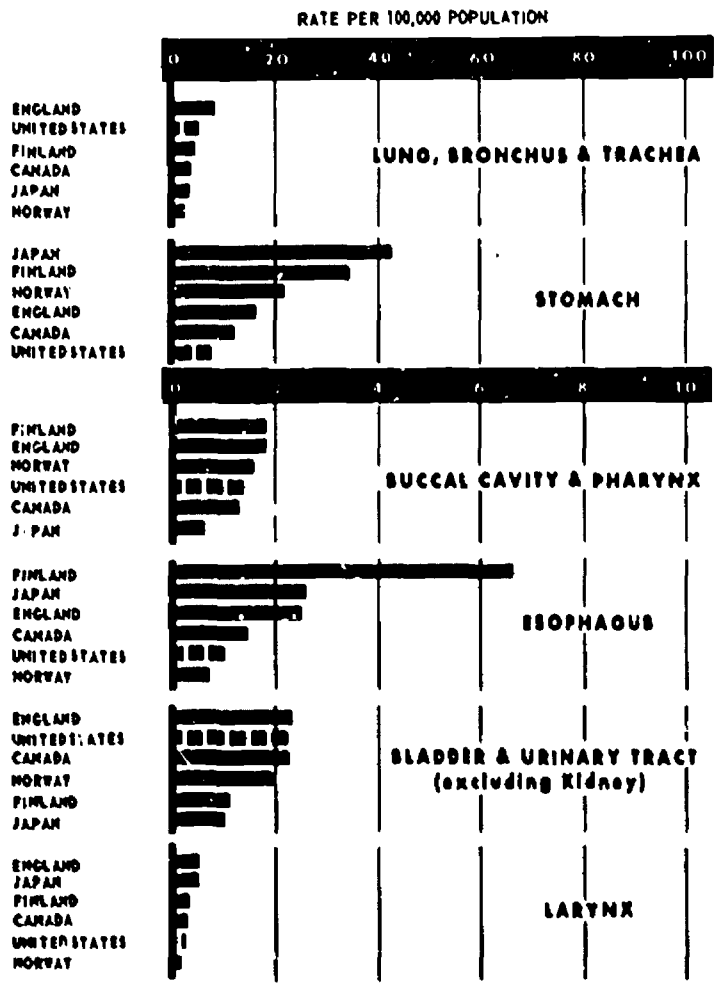


FIGURE 3B.

U.S. data age-adjusted to the total population of the continental United States 1950.
Source: Calculated from Segi, M., and Kurihara, M. (317).

individual sites, particularly those for which the five-year survival rates are very low. Figure 4, which contrasts recent mortality and incidence rates, demonstrates that these rates differ markedly only for sites with more favorable prognosis—oral cavity, prostate, and urinary bladder. These differences are compatible with existing information on the survival experience of cancer patients.

COMPARISON OF AGE-ADJUSTED MORTALITY RATES BY SEX IN THE UNITED STATES 1959-1961 WITH INCIDENCE RATES FROM STATE REGISTRIES - UPPER NEW YORK STATE 1958-1960 AND CONNECTICUT 1959.

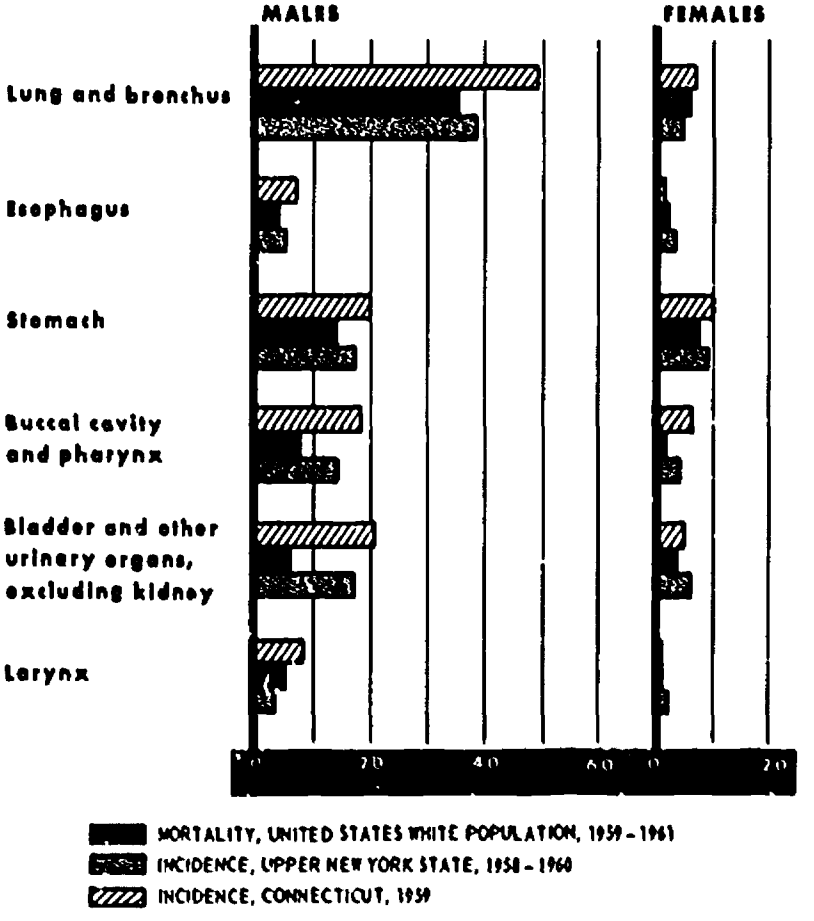


FIGURE 4.

Sources: Vital Statistics of the United States, annual volumes; Ferber, B. et al (112).
Eisenberg, H., personal communication to the Surgeon General's Advisory Committee on Smoking and Health.

The next sections describe some aspects of incidence or mortality for eight sites—lung and bronchus, larynx, oral cavity, esophagus, urinary bladder, kidney, stomach and prostate. Of these, six were selected for spe-

cial consideration because they are the ones most often reported by the prospective studies to have the highest mortality ratios of tobacco-users to non-users, and stomach was included because the trend in cancer of this organ in recent years has been in such marked contrast to that for cancer of the lung and bronchus.

Sex Ratio

The male-female ratios of age-adjusted death rates (U.S., 1959–61) (252) from cancer for the six sites common to both sexes are given below:

	Male/Female Ratio Whites	*Male/Female Ratio Nonwhites*
Larynx	10.8	7.6
Lung and bronchus	6.7	6.2
Oral cavity	3.8	3.3
Esophagus	4.1	4.2
Stomach	2.0	2.3
Urinary bladder	1.3	1.6

The ratios of male/female death rates vary with site: ranging from about 10 to 1 for larynx to much less than 2 to 1 for urinary bladder, the findings for white and nonwhite populations being in substantial accord. The male-female ratios for five of the six sites have remained quite stable over the past 30 years, lung cancer providing the important exception. The lung cancer sex ratio was 1.5 to 1 in 1930 and has steadily increased during the intervening period to the current value of over 6 to 1. Mortality, register and survey data yield consistent information on sex ratios, and material from the latter sources need not be reproduced here.

Geographic Variation

Cancers of the oral cavity, larynx, lung and bronchus, prostate, and urinary bladder do not exhibit any consistent marked regional departures from the over-all U.S. incidence and mortality experience (91, 130). Cancer of the esophagus is higher in the Northeast and North Central regions, and gastric cancer is encountered less frequently in the South than in other parts of the country. Within regions, some cities are known to display exceptional incidence of certain types of cancer (91).

Urban-Rural Gradients

The excess risk for residents of urban areas is most pronounced for cancer of the lung and bronchus, oral cavity, and esophagus. This urban excess is not characteristic of the data for stomach, prostate, or bladder (208).

Income Class

Information on income class gradients in cancer risks by site was secured in the morbidity surveys of ten U.S. metropolitan areas in 1947–48 (91).

According to this source, incidence was inversely related to income class for five sites under review—oral cavity, esophagus, stomach, larynx, lung. The rates for males in the lowest income class for esophagus and lung were about double those for high income males; the range for the remaining sites was not quite so pronounced, the excess in low income risks being on the order of 60–80 percent. For one site within the oral cavity, salivary glands, no relationship was found between incidence and income class. The inverse gradient by income class, while present, was much weaker among females for esophagus, stomach, and lung. The female risks for cancer of the oral cavity and the larynx were too small to permit meaningful statements on this topic. Incidence of bladder cancer was not related to income class for either males or females.

Occupation

From unpublished tabulations of deaths for 1950 according to occupation and industry prepared by the National Vital Statistics Division of the Public Health Service (252), it is possible to select certain occupations with unusually high mortality for specific sites. One of the more striking results is the liability of bartenders, waiters, and others engaged in the alcoholic beverage trade to oral and esophageal cancers, the mortality ratios being about double those for all males of comparable age. Similar findings have been reported by the Registrar-General of England and Wales (135).

Review of the distribution of lung cancer risks by occupation indicates a large variety of occupational groups in metal working trades, such as molders, boilermakers, plumbers, coppersmiths, sheet metal workers, etc., who are subject to a 70–90 percent excess risk for this site.

One feature which does not come through clearly in the rather crude occupational mortality data is the high risk of bladder cancer among workers exposed to aromatic amines, as established by observations on workers in individual plants (179, 336). The 50 percent excess of bladder cancer mortality of workers in chemical and allied industries, reported in vital statistics, must represent a dilution of higher risks in specific occupations in which the hazards are much greater. This dilution occurs because data from a number of industries and occupations, including many in which no particular bladder cancer hazards are present, are pooled in broad categories.

Ethnic Group

Foreign-born migrants to the United States as a group have age-adjusted death rates for cancer of the esophagus and stomach about twice those recorded for native-born white males and females. Lung cancer mortality is about one-third higher among the foreign-born, again for both sexes. No important differential between native- and foreign-born has been observed for oral cancers (both sexes) or for bladder (males); the rates for bladder cancer are about 30 percent lower for women born abroad than for women born in the United States. Laryngeal cancer has not been systematically studied from this point of view (144).

The several ethnic groups in the United States display their own characteristic patterns of excesses and deficits in risk by site. Men and women born in Ireland have high death rates for oral and esophageal cancers. The Polish-born Americans have pronounced excess mortality for esophageal and gastric cancers for both sexes, and Polish males rank first in lung cancer. The Russian-born, a large proportion of whom are Jews, show high death rates for stomach (both sexes) and a striking excess risk for esophageal cancer among women. The English-born American men and women have above-average lung cancer risks.

Trends

Figure 5 describes the divergent behavior in mortality trends for cancer, all sites, among men and women since 1930. The age-adjusted death rate has been declining slightly in females, but increasing in males; most of the rise for males is obviously attributable to the sustained upturn in lung cancer certifications.

The succeeding logarithmic graph (Figure 6) portrays trends in mortality among whites for individual sites; nonwhites have been excluded because the comparability of data over time for this group would be affected more seriously by recent improvements in quality of death certifications. Lung cancer mortality among males has risen at a fairly constant rate since 1930; for females the trend has also been consistently upward, but at a much slower pace. This form of cancer was responsible for the deaths of approximately 5,700 women and 33,200 men in the United States in 1961. As recently as 1955, the corresponding totals were 4,100 women and 22,700 men (252). The register and survey data also have reported a marked rise in lung cancer incidence. No other cancer site has exhibited in recent history a rate of increase, absolute or relative, approaching that recorded for lung cancer in males.

Inspection of age-adjusted mortality rates for oral cavity, esophagus, larynx, prostate, and urinary bladder cancers pinpoints no dramatic shift in risk. The rates for stomach cancer, however, have been declining steadily. This has led some observers to conjecture that the rise in lung cancer and the decline in stomach cancer may represent two aspects of the same phenomenon, a progressive transfer of deaths to lung cancer which might formerly have been certified as stomach cancer. Detailed examination of the data on possible compensatory effects by country, sex, age and other variables conclusively rules out diagnostic artifacts of this type as a possible explanation.

The Connecticut and New York State registers (112, 136) and the ten-city surveys (91) confirm the decline in gastric cancer and the absence of important changes over time for oral cavity, esophagus, urinary bladder, and kidney, and show a small increase for larynx. The registers also indicate a small rise in incidence of prostatic carcinoma; the age-adjusted rate in upstate New York increased from 21.4 in 1941–43 to 24.9 in 1958–60, and the Connecticut experience revealed a similar displacement. A possible reason for this increase in case reports of prostatic cancer to registers may be found in more careful examination by pathologists of prostates removed

TRENDS IN AGE-ADJUSTED MORTALITY RATES FOR CANCER BY SEX - ALL SITES AND RESPIRATORY SYSTEM IN THE UNITED STATES, 1930-1960. [1]

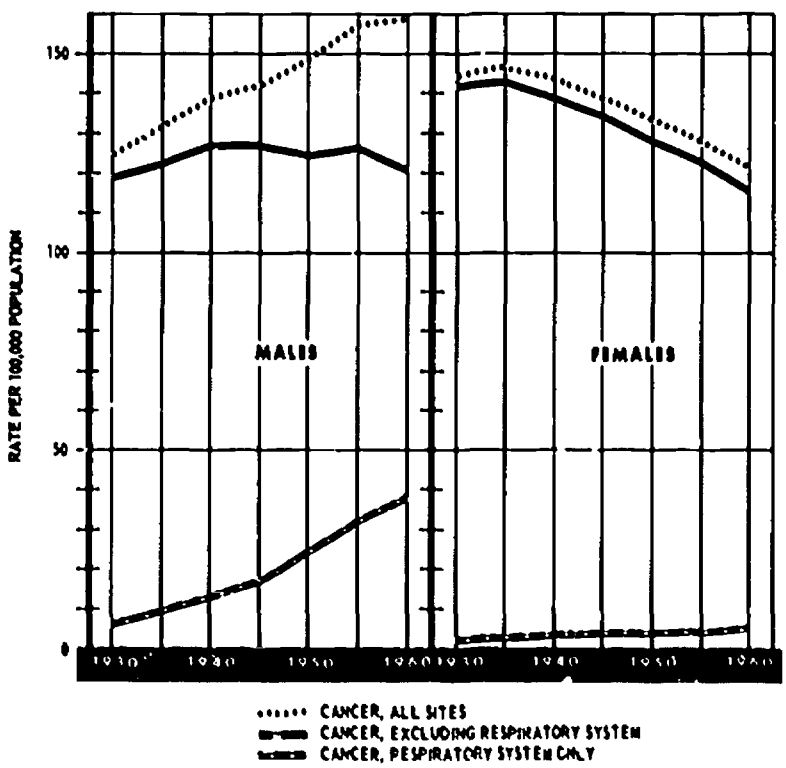


FIGURE 5.

Age-adjusted to the total population of the continental United States, 1950.

Source: Vital Statistics of the United States, annual volumes.

surgically, which would result in discovery and reporting of more asymptomatic prostatic carcinomas. The mortality data relate to clinically active prostatic carcinomas and in this instance probably give a more accurate assessment of changes over time than the registry data.

AGE-SPECIFIC MORTALITY FROM LUNG CANCER

The schedules of age-specific lung cancer mortality rates for males studied in five successive time periods from 1914 to 1960 are shown in Figure 7 (dotted lines). It can be seen that the rate rises to a maximum at age 70 and then declines gradually thereafter. Incidence data from cancer registers provide a close parallel (112).

TRENDS IN AGE-ADJUSTED MORTALITY RATES FOR SELECTED CANCER SITES BY SEX IN THE UNITED STATES, 1930-1960. [1]

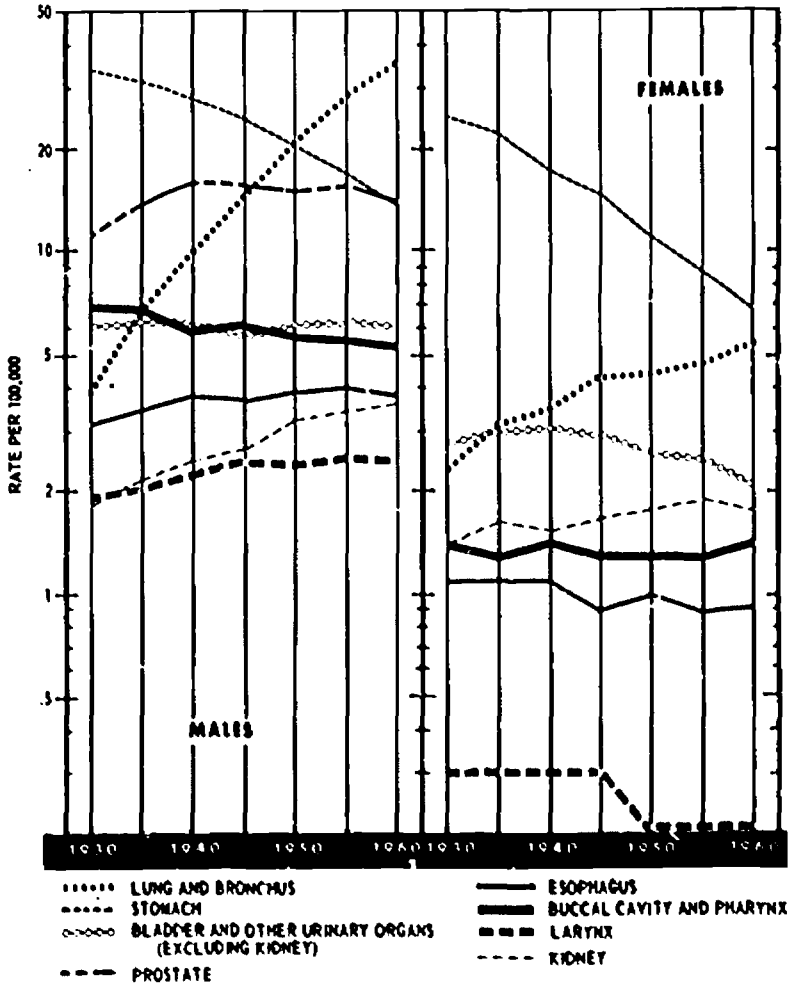


FIGURE 6.

Data are for the white population, age-adjusted to the total population of the continental United States, 1950.

Sources: Gordon T., et al. (130); and unpublished calculations of the Biometry Branch, National Cancer Institute, U.S. Public Health Service.

However, when any separate cohort (a group of persons born during the same ten-year period) is scrutinized over successive decades, the seeming downturn of mortality rates after age 70 can be seen to be an artifact due

AGE-ADJUSTED MORTALITY RATES FOR CANCER OF THE LUNG AND BRONCHUS BY BIRTH COHORT AND AGE AT DEATH FOR MALES, UNITED STATES 1914, 1930-32 , 1939-41, 1949-50, 1959-61. (1)

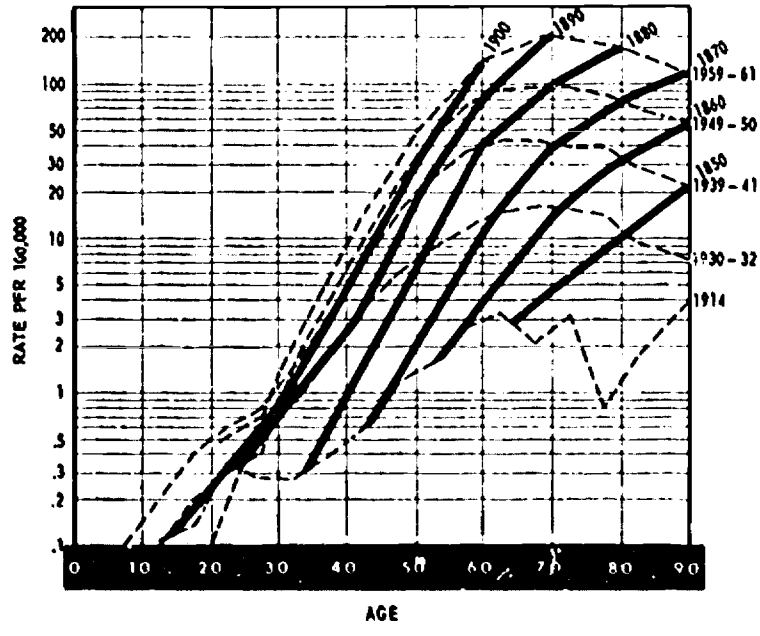


FIGURE 7.

Data are for the white population.

Sources: Dorn, H. F., and Cutler, S. J. (91).

Unpublished calculations of the Biometry Branch, National Cancer Institute, U.S. Public Health Service.

to the admixture of cohorts with differing mortality experiences. When the points representing mortality rates among members of the same cohort group are connected, from each dotted-line curve to the next, the new curve (each of the bold lines) represents the mortality rates over time for the members of a cohort. Thus, to cite the cohort born around 1880 as an example, the bold-line curve shows the mortality rates of the cohort in 1914 when its members were about 34 years old, in 1930–32 when they were about 51 years old, in 1939–41 when they were about 60 years old, in 1949–50 when they were about 70 years old, and in 1959–61 when they were about 80 years old.

The new series of curves, representing the mortality experience of the individual cohorts, reveal two important facts: (a) Within each cohort, lung cancer mortality increases unabated to the end of the life span; and (b) successively younger cohorts of males are at higher risks throughout life

AGE-ADJUSTED MORTALITY RATES FOR CANCER OF THE LUNG AND BRONCHUS BY BIRTH COHORT AND AGE AT DEATH FOR FEMALES, UNITED STATES 1914, 1930-32, 1939-41, 1949-50, 1959-61.[1]

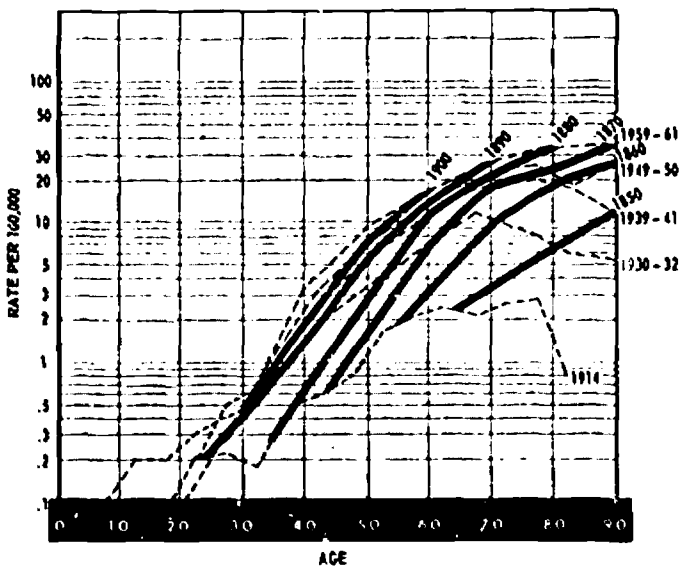


FIGURE 8.

Sources: Dorn, H. F., and Cutler, S. J. (91).

Unpublished calculations of the Biometry Branch, National Cancer Institute, U.S. Public Health Service.

than their predecessors. The increasing steepness of the slope of the cohort mortality curves, beginning with the 1850 cohort and examining the cohort curves from right to left, shows that the rise in lung cancer mortality is much more rapid in the recent cohorts. The pattern would suggest that the effects noted may be attributable to differences in exposure to one or more factors or to a progressive change in population composition among the several cohorts.

For women, incidence and mortality increase up to the older ages, when the rates fluctuate irregularly (Figure 8). A cohort approach to the female experience reveals only small displacements in rates between successive cohorts, the effects being smaller than those noted for males.

EFFECTS OF CHANGES IN LUNG CANCER DIAGNOSIS ON TIME TRENDS

The cause of death is at times difficult to establish accurately from clinical findings alone, and the incidence and mortality rates recorded for lung

cancer vary with the diagnostic criteria adopted (147, 148). A pathologic anatomic diagnosis provides the most reliable evidence for the classification of lung cancer deaths.

Shifts in diagnostic standards or in diagnostic errors must be considered in evaluating the trends in lung cancer mortality shown in tabulations prepared by the offices of vital statistics. In recent years, about two-thirds of the certifications of lung cancer deaths have been based on microscopic examination of tissue from the primary site and the percentage is even higher for deaths under 75 years (146, 247). The proportion of lung cancer certifications in the 1920's and 1930's based on comparable diagnostic evidence is unknown, but the figure was certainly much lower.

Gilliam (128) has attempted to evaluate the possible effects of diagnostic changes on the published lung cancer mortality statistics. He calculated that if two percent of the deaths certified to tuberculosis in 1914 were really due to lung cancer, the observed increase in bronchogenic carcinoma between 1914 and 1950 could be scaled down from 26- to 8-fold for males and from 7-fold to 1.3-fold for females. If 1930 or a later year had been used as the point of departure to estimate the effects of continued misdiagnoses of tuberculosis on this scale, the downward revision in the slope of the lung-cancer rates would have been much smaller. The improved accuracy of lung cancer diagnoses must be conceded, so that the issue remains a quantitative one: what part of the recorded increase can be accounted for by control of diagnostic variation? Retrospective adjustment of vital statistics from past years can yield only rough qualitative judgments (267), and we must rely on the composite evidence from several sources.

The following points have been advanced to support the thesis of a real increase in lung cancer (62):

(a) The rising ratio of male to female deaths

(b) The increasing mortality among successively younger cohorts

(c) The magnitude of the increase in mortality in recent years

To this we would add that the question can be resolved by reference to the contemporary experience of large, population-based cancer registers for which a high percentage of the cases reported have microscopic confirmation. Sufficient time has now elapsed to permit the tumor registries in Connecticut (136) and New York (112) to supply convincing evidence for a true increase in lung cancer. Diagnostic comparability is a far less important consideration in the review of data collected by cancer registries. Between 1947 and 1960 there were no significant advances in diagnostic methods (exfoliative cytology studies of the sputum have been used for diagnostic purposes since 1945). In upstate New York the age-adjusted incidence of lung cancer per 100,000 males rose from 17.8 in 1947 to 41.0 in 1960 and for females from 3.2 to 4.9. These figures imply an average annual rate of increase of about 7 percent for males and 3–3.5 percent for females during this interval.

For earlier years the relative frequency data from necropsy series contribute valuable information. The records of large general hospitals where diagnostic accuracy of lung cancer has been uniform and excellent for many years also support the thesis of a real increase in lung cancer. Institutions such as the University of Minnesota Hospitals (Minneapolis) (350), Presby-

terian Hospital (New York City) (323), and the Massachusetts General Hospital (Boston) (54), now find many more lung cancers than in the past. In the Massachusetts General Hospital, for example, only 17 cases of bronchogenic carcinoma, 11 males and 6 females, were diagnosed in 5,300 autopsies from 1892 to 1929 (autopsy rate of 33 percent), compared to 172 cases, 140 males and 32 females, in 5,000 autopsies from 1956 to 1961 (autopsy rate of 68 percent). This American experience is consistent with that reported abroad, where virtually all patients dying in certain hospital services have been subjected to autopsy for many years. Steiner (328) summarized several such series and Cornfield et al. (62) returned to the original sources and found the collective evidence to affirm a rise in the percent of lung cancers found at necropsy from 1900 on.

The Copenhagen Tuberculosis Station data, reviewed by Clemmesen et al. (56), present an unusual opportunity for evaluating the effect of improvement in diagnosis on the time trend. In the Copenhagen tuberculosis referral service, used extensively by local physicians, where diagnostic standards and procedures including systematic bronchoscopy remained virtually unchanged between 1941 and 1950, the lung cancer prevalence rate among male examinees increased at a rate comparable to that recorded by the Danish cancer registry for the total male population.

The rising trend for lung cancer during the past 15 years thus is well documented. The increasing frequency of lung cancer found at necropsy from 1930 onward, while of itself not decisive, when considered in the light of recent events reported by cancer registers, would support the conclusion that the rise in lung cancer did not begin in the 1940 decade, but was a continuation of a trend begun earlier.

CARCINOGENESIS

Tobacco and tobacco smoke contain a complex mixture of hundreds of different chemical components among which are (a) numerous *polycyclic aromatic hydrocarbons* and (b) *inorganic compounds*. Many of these compounds have been shown to be carcinogenic in animals. For information on other components of tobacco and tobacco smoke see Chapter 6.

Before considering the biological evidence available for the carcinogenic effect of these components of tobacco and tobacco smoke, it may be helpful to review briefly some basic principles of carcinogenesis.

Fundamental Problems in Carcinogenesis in Relation to Induction of Neoplastic Changes in Man by Tobacco Smoke

Carcinogenesis is a complex process. Many factors are involved. Some are related to the host, others to the agents. The host factors include genetic, strain, and organ differences in sensitivity to given agents; hormonal and other factors which modify sensitivity of cells; and nutritional state (123).

The character of the agents involved in carcinogenesis varies greatly. Some agents by themselves cause irreversible alterations in cells which may

lead to the production of cancer; others promote the carcinogenic process (21, 33). The former are called *initiators*, the latter *promoters*. Some substances, such as urethan, can be both.

Several classes of chemicals are known to be capable of inducing cancers (143). The chemical properties, the physical state of a substance, and the vehicle in which the substance is introduced into the body can influence the carcinogenic potency of environmental agents, e.g., insertion of a plastic membrane into tissues can cause a cancer (2, 261, 347), but a fine powder of the same plastic has not done so (257). Carcinogens vary with respect to organ affinity and mechanism of inducing a neoplastic change.

There is mounting evidence that viruses may also play an important role in the induction of tumors (137, 140, 345).

It follows from these considerations that failure to produce cancer in a given test, by a given material, does not rule out the carcinogenic capacity of the same material in another species or in the same species when applied under different circumstances. Conversely, induction of cancer by a compound in one species does not prove that the test compound would be carcinogenic in another species under similar circumstances. Therefore, tests for carcinogenicity in animals can provide only supporting evidence for the carcinogenicity of a given compound or material in man. Nevertheless, any agent that can produce cancer in an animal is suspected of being carcinogenic in man also.

The types of cancers produced by the polycyclic aromatic hydrocarbons and other carcinogens depend on the tissues with which they make contact.

Carcinogenesis can be initiated by a rapid single event, best exemplified by the carcinogenic effect of a split-second exposure to ionizing radiations (e.g., from atomic detonation) (40, 351). More often, however, it appears to be characterized by a slow multi-stage process, preceded by non-specific tissue changes, as exemplified by cancers arising in burns. Evidence is presented in another section of this Report that cancer of the lung in cigarette smokers, as well as experimental cancer induced by presumed carcinogens in smoke, is preceded by distinct histologic alterations which can progress to the development of "cancer in situ." These need not proceed to the formation of invasive cancer, and may regress following removal of the stimulus.

The character of "precancerous" change varies in different organs, e.g., in the bladder it is manifested by the formation of "benign" papillomas; in the oral cavity, by the formation of white patches of thickened squamous epithelium—leukoplakia—a non-neoplastic reversible change. The evolved cancer is also subject to further changes. Often, rapidly growing variants develop, a process termed *progression* (119).

Almost every species that has been adequately tested has proved to be susceptible to the effect of certain polycyclic aromatic hydrocarbons identified in cigarette smoke and designated as carcinogenic on the basis of tests in rodents. Therefore, one can reasonably postulate that the same polycyclic hydrocarbons may also be carcinogenic in one or more tissues of man with which they come in contact.

Experimental studies have demonstrated the presence of substances in tobacco and smoke which themselves are not carcinogenic, but can promote

carcinogenesis or lower the threshold to a known carcinogen. There is also some evidence for the presence of anticarcinogenic substances in tobacco and tobacco smoke (107).

Threshold

In any assessment of carcinogenicity, dosage requires special consideration. The smallest concentration of benzo(a)pyrene known to induce carcinoma when dissolved in acetone and applied to the skin of mice three times weekly is 0.001 percent (380). Subcutaneous cancer follows injection of only 0.00195 mg. of benzo(a)pyrene in 0.25 ml. tricaprylin. Whether there is a threshold for effective dosage of a carcinogenic agent is controversial at the present time. The evidence for the existence of a threshold has been summarized by Brues (43). When pulmonary tumors were induced in mice with dibenzanthracene and urethan by Heston et al. (172, 232), a linear response was demonstrated at higher doses but a curvilinear response appeared at lower doses. At extremely low dosage, the possible effect of the agent became obscured by the incidence of spontaneous pulmonary tumors. In the case of induction of cancer by ionizing radiation, it has been claimed that there is no threshold (210). It is conceivable that there is no threshold for certain neoplasms, whereas there may be one for others.

Neither the available epidemiologic nor the experimental data are adequate to fix a safe dosage of chemical carcinogens below which there will be no response in man (43, 172, 210, 232).

Carcinogenicity of Tobacco and Tobacco Smoke in Animals

There is evidence from numerous laboratories (31, 42, 92, 93, 105, 132, 139, 263, 296, 297, 338, 372, 373, 382, 383) that tobacco smoke condensates and extracts of tobacco are carcinogenic for several animal species. Several laboratories obtained negative results (154, 262, 267, 268).

The nature of the test system is critical in studies on carcinogenic activity of such complex mixtures. The relatively high susceptibility of mouse skin to carcinogenic hydrocarbons has made it a favorite test object (6, 278). A second test system also used is the induction of pulmonary adenomas in mice. This will be detailed in the section on Experimental Pulmonary Carcinogenesis. A third system which has been used less frequently is the induction of subcutaneous sarcomas in the rat whose connective tissues have been found to be susceptible to the carcinogenic action of many different chemicals as well as of complex materials. Another test, which has been used in some studies and can be read within five days after painting the skin of mice with a carcinogen, consists of determining the number of sebaceous glands and the thickness of the epidermis (342a). However, the reliability of this procedure as a bio-assay for carcinogenesis is open to question.

Skin

Many investigators have shown that the application of tobacco tar to the skin of mice and rabbits induces papillomas and carcinomas (31, 42, 92, 93,

105, 132, 139, 263, 296, 297, 338, 372, 373, 382, 383). Wynder et al. (382) applied a 50 percent solution of cigarette smoke condensate in acetone three times weekly to the shaved backs of mice so that each received about 10 gm. yearly. The animals were usually painted for 15 months. More than 5 gm. annually was required for the induction of epidermoid carcinoma and more than 3 gm. for the induction of papillomas (372, 373). Since the carcinogenic potency of a smoke condensate can be altered by varying conditions of pyrolysis, the manner of preparation of the tar is of importance (392). This may be one reason for the negative reports (154, 262, 267, 268) encountered in the literature. Extracts of tobacco usually have weaker carcinogenic activity than do the condensates of cigarette smoke (93, 390).

Gellhorn (126) and Roe et al. (290, 293) have reported that condensates of cigarette smoke have cocarcinogenic or promoting properties. It was found that the application of a mixture of benzo(a)pyrene plus condensate of cigarette smoke to the skin of mice resulted in the production of many neoplasms, whereas the same concentration of benzo (a) pyrene alone failed to elicit tumors. Gellhorn (126) found that the tobacco smoke condensate appeared to accelerate the transformation of papillomas to carcinomas. Anticarcinogens have also been reported in condensates of cigarette smoke (107).

Nicotine is not usually considered a carcinogen on the basis of animal experiments (346, 391). Removal of nicotine or other alkaloids did not diminish the carcinogenicity of condensates of smoke for the skin of mice. The induction of pulmonary adenomas in mice by urethan (120) and of skin tumors in mice by ultraviolet radiation (121) are not altered by the administration of nicotine or some of its oxidation products.

Subcutaneous Tissue

Druckrey (92) found that cigarette smoke condensates or alcoholic extracts of cigarette tobacco regularly induced sarcomas in rats at the site of subcutaneous injections. The material was injected once weekly for 58 weeks, the total dose administered being 3.2 gm. The animals were followed, thereafter, until death. Approximately 20 percent of the animals in each experiment developed the neoplasms. Druckrey also carried out similar experiments with benzo(a)pyrene and found that the amount of this polycyclic aromatic hydrocarbon in smoke condensates or tobacco extracts cannot account for more than a few percent of the activity of the tobacco products. This same discrepancy between the quantity of benzo(a)pyrene in smoke condensates and the carcinogenic potency of the condensates has been reported by several investigators using the mouse skin test (92, 93, 126, 372, 390).

Mechanism of the Carcinogenicity of Tobacco Smoke Condensate

Tobacco smoke contains many carcinogenic polycyclic aromatic hydrocarbons (Table 2, Chapter 6). Benzo(a)pyrene is present in much larger concentrations than is any other carcinogenic polycyclic hydrocarbon. The inability to account for the carcinogenicity of the tobacco products, except to a very minor degree, by the amount of benzo(a)pyrene present was unanticipated. Both Druckrey (92) and Wynder (372) emphasized that

the benzo(a)pyrene concentration of various tobacco and smoke preparations is only sufficient to account for a very small part of the carcinogenicity of these materials. One hypothesis suggests that promoting agents present in tobacco and tobacco smoke, such as various phenols, enhance the potency of the carcinogenic hydrocarbons so as to account for the biological activity of the tobacco products. Further, possible synergism between low levels of the several known carcinogens in the tobacco condensates and extracts may also enhance the carcinogenic potency.

Other Materials of Possible Importance in Carcinogenicity

PESTICIDES

Pesticides currently used in the husbandry of tobacco in the United States include DDT, TDE, aldrin, dieldrin, endrin, chlordane, heptachlor, malathion and occasionally parathion (see Chapter 6). The first two are used more commonly than the others nearer the time for harvesting. TDE has been detected in tobacco and its smoke (242), and endrin has been extracted from tobacco on the market (34, 35). Aldrin and dieldrin have been found to increase the incidence of hepatomas in mice of the C3HeB/Fe strain (68). Aldrin is metabolized to dieldrin, and the effect may be due only to the latter or some subsequent metabolite. DDT has been shown to induce hepatomas in trout (153) and rats (253). The possible role of these compounds in contributing to the potential carcinogenicity of tobacco smoke is not known (see also Chapter 6, section on Pesticides).

LACTONES

The lactones have been suggested as contributors to the carcinogenic effects of tobacco. Attention was focused on these compounds by the discovery (74, 74A, 291, 292, 362) that β-propiolactone, used as a sterilant and preservative, is carcinogenic for mice. Coumarin, a δ-lactone, has been used as a common flavoring in tobacco. Hydroxy- and methoxy-coumarins are constituents of the leaf itself and are carried over in the smoke. Also the γ-lactone, β-levantenolide, is present in both tobacco and smoke (354). The following lactones (not suggested to be present in tobacco) have been found to be carcinogenic for animals: γ-lactones (patulin, penicillic acid, methyl protoanemonin) and δ-lactones (parasorbic acid lactone and aflatoxins).

RADIOACTIVE COMPONENTS

Potassium 40, a β-emitter, has been reported to be a source of radioactivity in cigarette smoke. The amounts of this activity taken into the lung, even by the heavy smoker, are minute when compared with the daily uptake of K 40 from the diet. Furthermore this material is highly soluble and it is rapidly eliminated from the lung tissue thereby preventing any local build-up (300a). The α-particle activity due to the radium and thorium content of tobacco smoke, even for the heavy smoker, is less than one percent of the atmospheric radon and thoron inhaled daily by any individual (347a). A recent but still unpublished report holds that Po 210 is the major source of radioactivity in cigarette smoke. The amounts calculated to be absorbed are high enough to merit further study as a possible factor in carcinogenesis (282a). No data

appear to have been published on the uptake by the tobacco plant of radioactive constituents from fall-out (e.g., Strontium 90 and Cesium 137).

Summary

Condensates of tobacco smoke are carcinogenic when tested by application to the skin of mice and of rabbits, by subcutaneous injection in rats, and by painting the bronchial epithelium of dogs. The amount of known carcinogens in cigarette smoke is too small to account for their carcinogenic activity. Promoting agents have also been found in tobacco smoke but the biological action of mixtures of the known carcinogens and promoters over a long period of time is not understood.

Carcinogenesis in Man

Despite the many uncertainties in the application to man of research results in animals, the animal data serve a purpose in indicating potential carcinogenicity. The greatest consistency is observed in respect to those groups of chemical compounds which are carcinogenic in many species. Several of the polycyclic aromatic hydrocarbons present in tobacco smoke fall into this category in that they are carcinogenic for most animal species tested. Since the response of most human tissues to exogenous factors is similar qualitatively to that observed in experimental animals, it is highly probable that the tissues of man are also susceptible to the carcinogenic action of some of the same polycyclic aromatic hydrocarbons. The results of exposing humans to pure polycyclic aromatic hydrocarbons or to natural products containing such compounds have been reviewed by Falk et al. (108).

Polycyclic Aromatic Hydrocarbons

Cancer induction in man by the application of "pure" polycyclic aromatic hydrocarbons has not been reported. Klar (188) reported an epithelial tumor on his left forearm that appeared three months after termination of an experiment in which mice were painted with 0.25 percent benzo(a)pyrene in benzene. Cottini and Mazzone (63) applied 1.0 percent benzo(a)pyrene in benzene to the skin of 26 volunteers in daily doses and observed the sequential development of erythema, pigmentation, desquamation, and verrucae. The changes were more pronounced in older than in younger volunteers. After 120 applications, the experiment was terminated and the lesions regressed within three months. Rhoads et al. (286) described similar changes in human skin painted with the same carcinogen. These reversible changes were similar to the initial changes in the skin of men who ultimately developed invasive cancers following industrial exposure to carcinogens. Cancer of the skin of the fingers has not been reported in cigarette smokers, despite the intense discoloration so often seen at this site (212). However, spontaneous cancer of the skin of the fingers is very rare.

Industrial Products

SOOT

Cancer of the scrotum in chimney sweeps subjected to prolonged massive exposure to soot was a common finding in the eighteenth century (279). As many as one in every ten men engaged in this occupation developed cancers (204). Sporadic cases of cancer of the skin at other sites, such as the face (60), the ear, and the penis (264), were also described. The neoplasms usually occurred in men between 18 and 47 years of age (213), possibly reflecting the early age at which boys entered this occupation. Whether there is an increase in cancer in persons *now* working in industries involving exposure to "carbon black" is being debated (108). The chemical and physical properties of "carbon black" vary widely (109, 110).

As early as 1922, Passey (266) found that cancer of the skin could be produced experimentally by extracts of soots. More recently, Falk et al. (111) showed that polycyclic hydrocarbons in the "carbon black" were present in processed rubber, and rubber extracts were found to be carcinogenic for the skin of mice. Also Falk and Steiner (109, 110) found furnace-type black rich in pyrene, fluoranthene, benzo(a)pyrene, benzo(e)pyrene, anthanthrene, benzo(g, h, i)perylene, and coronene in particles having an average diameter of 80 mμ or larger. These compounds were not present in channel blacks which have smaller particle size. The amount of benzo(a)pyrene extracted from different soots varies from none to 2 mg. per gm. (307).

COAL TAR AND PITCH

Butlin (50) in 1892 described cancer of the skin as an occupational hazard in the coal tar industry. The distillation of coal tar yields many different organic compounds with a residue of pitch containing polycyclic aromatic hydrocarbons (300). Henry (166) reported that up to 1945, 2,229 of 3,753 cases of industrial skin cancer studied were attributed to exposure to tar and pitch, the remainder to mineral oils. The latent period for induction of this type of cancer is estimated to be 15 to 25 years. Most reports about this type of cancer have come from England (166), but they have also appeared from other countries (44, 73, 231, 310). Bonnet (32) reported an interesting case of pulmonary cancer in a workman exposed to hot tar containing three percent benzo(a)pyrene. He estimated that 320 μg. of the carcinogenic hydrocarbon could have been inhaled hourly. Carcinogenicity of both creosote oil and anthracene oil for the skin of workmen has been documented (18, 39, 259).

MINERAL OILS

So-called paraffin cancer is not caused by paraffin but by exposure to impurities in oils used in the process of purification (165, 203). Recent work (321) has confirmed the view that refined paraffin wax does not contain polycyclic aromatic hydrocarbons and that it is not carcinogenic.

The danger incidental to exposure to mineral oils has been decreased by extraction of carcinogenic hydrocarbons with sulfuric acid (164). Bioassay of mineral oils indicates that their content of carcinogens varies with their

geographic origin (348). Animal tests show that the carcinogenicity of mineral oil increases as the temperature of distillation increases or when cracking is instituted for the formation of new compounds. A variety of carcinogenic compounds has been isolated from different fractions. Some fractions presumably free from benzo(a)pyrene have nevertheless been found to be carcinogenic. Coal tar contains 0.3 to 0.8 percent benzo(a)-pyrene, soot 0.03 percent, and American shale oil 0.003 to 0.004 percent (51).

SUMMARY

There is abundant evidence that cancer of the skin can be induced in man by industrial exposure to soots, coal tar and pitch, and mineral oils. All of these contain various polycyclic aromatic hydrocarbons proven to be carcinogenic in many species of animals. Some of these hydrocarbons are also present in tobacco smoke. It is reasonable to assume that these can be carcinogenic for man also.

CANCER BY SITE

The seven prospective studies described and summarized in Chapter 8 provide a natural point of departure for considering the relative risks, for smokers and non-smokers, of cancer at specific sites. The consolidated findings (Table 1) identify eight sites as displaying higher risks of cancer among cigarette smokers, who in recent decades have been the predominant consumers of tobacco. These sites are lung, larynx, oral cavity, esophagus, urinary bladder, kidney, stomach, and prostate. The mortality ratios for cigarette smokers *vis-a-vis* non-smokers range in descending order from nearly 11 to 1 for cancer of the lung and bronchus to 1.3 to 1 for prostatic cancer. For five of these sites—lung, larynx, oral cavity, esophagus, and urinary bladder—cigarette smokers have a substantially higher cancer risk than non-smokers.

The smaller excess risks among cigarette smokers for cancer of the stomach, prostate, and kidney deserve comment. The prospective studies are not in complete accord as to an association with smoking history for cancer of the prostate and kidney, and in some of the studies which were conducted with other objectives in mind, the relationships of prostatic and renal cancer with smoking history represent incidental findings. No other evidence can be adduced in evaluating and interpreting the prostatic and renal mortality ratios, since the effects were not large enough to draw the attention of investigators. For these reasons, cancer of the prostate and kidney will not be discussed further at this time. This decision does not imply a conclusion that the findings must be artifacts, but rather that judgment on these sites should be suspended until more data become available.

The case for considering cancer of the stomach in more detail is not much stronger than for prostate and kidney, but the consistency among the prospective studies is better. In addition, the studies report a stronger association of smoking history with stomach ulcer. Clinical impressions of this relation-

TABLE 1.—*Expected and observed deaths and mortality ratios of current smokers of cigarettes only, for selected cancer sites, all other sites, and all causes of death; each prospective study and all studies*

Site of cancer		British doctors	Men in 9 States	United States veterans	California occupational [1]	California Legion [1]	Canadian veterans	Men in 25 States [1]	Total
Lung and bronchus, 162-3 [2]	Observed	129	233	519	138	98	317	399	1,833
	Expected	6.4	23.4	43.3	8.7	19.9	27.1	41.5	170.3
	Ratio	20.2	10.0	12.0	15.9	4.9	11.7	9.6	10.8
Larynx, 161	Observed	7	17	14	3	6	5	23	75
	Expected	0.0	1.3	2.4	0.0	4.0	0.0	6.3	14.0
	Ratio	.....	13.1	5.8	.....	1.5	.....	3.7	5.4
Oral Cavity, 140–8.	Observed	6	22	54	7	10	20	33	152
	Expected	0.0	7.8	8.1	7.2	5.2	5.1	3.6	37.0
	Ratio	.....	2.8	6.6	1.0	1.9	3.9	9.2	4.1
Esophagus, 150	Observed	7	18	33	4	9	22	20	113
	Expected	3.3	2.7	5.2	5.5	1.8	6.8	8.4	33.7
	Ratio	2.1	6.6	6.4	0.7	5.1	3.3	2.4	3.4
Bladder, 181	Observed	12	41	55	13	7	38	50	216
	Expected	13.9	17.2	31.4	2.2	1.8	22.3	22.8	111.6
	Ratio	0.9	2.4	1.8	6.0	4.0	1.7	2.2	1.9
Kidney, 180	Observed	8	21	34	10	6	13	28	120
	Expected	0.0	14.0	23.1	0.0	8.3	9.5	24.1	79.0
	Ratio	.....	1.5	1.5	.....	0.7	1.4	1.2	1.5
Stomach, 151	Observed	31	76	90	24	25	76	91	413
	Expected	28.3	33.7	61.5	31.4	20.5	41.2	68.6	285.2
	Ratio	1.1	2.3	1.5	0.8	1.2	1.9	1.3	1.4
Prostate, 177	Observed	15	51	106	4	19	48	75	318
	Expected	29.0	32.4	53.7	8.6	22.1	32.3	74.9	253.0
	Ratio	0.5	1.6	2.0	0.5	0.9	1.5	1.0	1.3
All Other Sites	Observed	116	290	671	141	106	237	571	2,132
	Expected	112.0	228.3	505.7	109.4	120.6	192.1	423.8	1,692.0
	Ratio	1.0	1.3	1.3	1.3	0.9	1.2	1.3	1.3
All Causes of Death.	Observed	1,672	3,781	7,236	1,456	1,264	4,001	6,813	26,223
	Expected	1,161.8	2,227.7	4,043.1	818.5	799.4	2,420.1	4,183.3	15,653.9
	Ratio	1.44	1.70	1.79	1.78	1.58	1.65	1.63	1.68

[1] Includes all cigarette smokers (current and ex-smokers).
[2] International Statistical Classification number.

ship undoubtedly stimulated some of the case-control studies of smoking and stomach cancer which have been reported. Stomach cancer incidence and mortality have been declining rapidly in the United States in recent years, simultaneously with the rise in lung cancer. This and the presence of additional evidence from retrospective studies justify reviewing stomach cancer in more detail in this chapter.

Thus the six cancer sites to be reviewed here are lung, larynx, oral cavity, esophagus, urinary bladder, and stomach.

LUNG CANCER

Historical

The earliest suspicions of an association between smoking and lung cancer were undoubtedly evoked by the provocative clinical observations that lung cancer patients were predominantly heavy smokers of tobacco. Early investigators, including Müller (250) in 1939 and Schairer and Schoeniger (309)

in 1943, were impressed not only with the clinical observations of a high proportion of tobacco smokers among lung cancer patients but also with the rise in the percentage of lung cancers in autopsy series in Cologne and Jena. Among the early observations in the United States were those of Ochsner and DeBakey (258) who were impressed by the probable relationship between cigarette smoking and lung cancer. The initial observations prior to Müller's work were not, however, corroborated by surveys including controls without lung cancer.

As early as 1928, Lombard and Doering (221) in a study of cancer patients' habits in Massachusetts, wrote that "any study of the habits of individuals with cancer is of little value without a similar study of individuals without cancer." Their analysis of 217 cases of cancer and 217 controls identified, among other things, an association between heavy smoking (all types combined) and cancer in general, and between pipe smoking and oral cancer in particular. The pipe smokers then constituted the bulk (73.1 percent) of the heavy smokers. This is of historical interest in relation to the present-day percentage of heavy cigarette smokers. Furthermore, since there were but five lung cancers in Lombard's test group in an era before much of the rise in lung cancer incidence had occurred, the data were not adequate to demonstrate an association between lung cancer and cigarette smoking.

Probably the first study designed to explore this association systematically was by Müller in 1939 (250) who had noted the increase in percentage of primary carcinomas of the lung being diagnosed at autopsy between the years 1918 and 1937 in Cologne, an increase almost entirely in males. Although considering other variables as possibly related to the rise in lung cancer mortality, such as increases in street dusts, automobile exhaust gases, war gas exposure in World War I, increased use of X-rays, influenza, trauma, tuberculosis, and industrial growth (air pollution?), he took special cognizance of the preponderant increase of lung cancer among males and the parallel rise in tobacco consumption from shortly before and since World War I and selected this variable for study. In what appears to be a carefully conducted inquiry of smoking habits in a series of 86 lung cancer patients and 86 apparently healthy controls, matched by age, a significant excess of heavy smokers was observed among the lung cancer patients.

In the next ten years, three more case-control studies or comparisons with cancers of other sites reached the literature (280, 309, 363) and from 1950 to the present time 25 additional retrospective (38, 82, 138, 147, 150, 152, 192, 199, 207, 211, 222, 236, 238, 277, 283, 301, 311, 314, 316, 335, 337, 365, 375, 379, 381) and 7 prospective studies (25, 83, 84, 87, 88, 96, 97, 157, 162, 163) were undertaken.

Retrospective Studies

The 29 retrospective studies of the association between tobacco smoking and lung cancer are sumarized in Tables 2 and 3. As these tables suggest, the studies varied considerably in design and method. Methodologic variations have occurred in the omission, inclusion, or treatment of the following:

METHODOLOGIC VARIABLES

Subject Selection—

1. Males and/or females
2. Occupational groups
3. Hospitalized cases
4. Autopsy series
5. Total lung cancer deaths in an area
6. Samplings of nationwide lung cancer deaths

Control Selection—

1. Age matching vs. age groups
2. Healthy individuals
3. Patients hospitalized for other cancers
4. Patients hospitalized for causes other than cancer
5. Deaths from cancers of other sites
6. Deaths from other causes than cancer
7. Samplings of the general population

Method of Interviewing—

1. Mailed questionnaires
2. Personal interviewing of subjects (or relatives) and controls
   a) By professional personnel
   b) By non-professional personnel

Tobacco-use Histories—

1. By type of smoking (separately and combined)
2. By amount and type
3. By amount, type, and duration
4. By inhalation practices

Other Variables Concurrently Studied—

1. Geographic distribution
   a) Regional
   b) Urban-rural
2. Occupation
3. Marital status
4. Coffee and alcohol consumption
5. Other nutritional factors
6. Parity
7. War gas exposures
8. Other pathologic conditions
9. Hereditary factors
10. Air pollution
11. Previous respiratory conditions

This listing of methodologic variations is by no means complete, nor does it imply that the individual retrospective studies should be criticized for their choice of study methods and factors for observation. The individual points of criticism have usually applied to one or two studies but not to all.

It is indeed striking that every one of the retrospective studies of male lung cancer cases showed an association between smoking and lung cancer. All have shown that proportionately more heavy smokers are found among the lung cancer patients than in the control populations and proportionately fewer non-smokers among the cases than among the controls. Furthermore, the disparities in proportions of heavy smokers between "test" groups and controls are statistically significant in all the studies. The differences in proportions of non-smokers among the two groups are also statistically significant in all studies but one (236); in the latter study, although there were fewer non-smokers among lung cancer patients, the difference was very small.

In the studies which dealt with female cases of lung cancer, similar findings are noted in all of them with one exception (238). In this latter study, although significantly more heavy smokers were found among the lung cancer cases than among the controls, the proportion of non-smokers among the cases was distinctly higher than among the controls. This is the only inconsistent finding among all the retrospective studies. Its meaning is not clear but the authors have indicated that non-response among their female cases was 50 percent.

The weight to be attached to the consistency of the findings in the retrospective studies is enhanced when one considers that these studies exhibit considerable diversity in methodologic approach.

TABLE 2.—*Outline of methods used in retrospective studies of smoking in relation to lung cancer*

Investigator, year, and reference	Country	Sex of cases	Number of persons and method of selection		Collection of data
			Cases	Controls	
Müller 1939 (250)	Germany	M	86 Lung cancer decedents, Bürger Hospital, Cologne.	86 Healthy men of the same age	Cases: Questionnaire sent to relatives of deceased. Controls: Not stated.
Schairer and Schoeniger 1943 (309).	Germany	M	93 Cancer decedents autopsied at Jena Pathological Institute, 1930–1941.	270 Men of the city of Jena aged 53 and 54 (average age of lung cancer victims=53.9).	Cases: Questionnaire sent to next of kin (195 for lung cancer). Controls: Questionnaire sent to 700.
Potter and Tully 1945 (280)	U.S.A.	M	43 Male patients aged over 40 in Massachusetts cancer clinics with cancer of respiratory tract.	1,847 Patients of same group with diagnoses other than cancer.	Cases and controls interviewed in clinics
Wassink 1948 (363)	Netherlands	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 (311)	U.S.A.	M	82 Male lung cancer cases among 5,003 patients recorded, 1941–48.	522 Miscellaneous tumors other than lung, larynx and pharynx.	Smoking habits recorded during routine hospital interview.
Mills and Porter 1950 (237)	U.S.A.	M	444 Respiratory cancer decedents in Cincinnati, 1940–45 and in Detroit, 1942–46.	430 Sample of residents matched by age in Columbus, Ohio, from census tracts stratified by degree of air pollution.	Cases: Relatives queried by mail questionnaire or personal visit. Controls: House-to-house interviews.
Levin et al., 1950 (207)	U.S.A.	M	236 Cancer hospital patients diagnosed lung cancer.	481 Patients in same hospital with non-cancer diagnoses.	Cases and controls: Routine clinical history taken before diagnosis.
Wynder & Graham 1950 (381).	U.S.A.	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.
McConnell et al., 1952 (236)	England	M–F	100 Lung cancer patients, unselected, in 3 hospitals in Liverpool area, 1946–49.	200 Inpatients of same hospitals, matched by age and sex, without cancer, 1948–50.	Personal interviews by the authors of both cases and controls, with few exceptions.
Doll and Hill 1952 (82)	Great Britain.	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 (301)	U.S.A.	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.

Wynder and Cornfield 1953 (379).	U.S.A.	M	63 Physicians reported in A.M.A. 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 (192)	Finland	M–F	812 Lung cancer patients diagnosed at one hospital in 16 years.	300 Outpatients of same hospital aged over 40, living in similar circumstances, and without cancer, February and March 1952.	Cases and controls questioned about smoking habits when taking case histories.
Lickint 1953 (211)	Germany	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 same sex and age range as cases.	Personal interviews by staff members of cooperating hospitals and clinics, corresponding in time to interviews of cases.
Brealow et al., 1954 (38)	U.S.A.	M–F	518 Lung cancer patients in 11 California hospitals, 1949–52.	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 (365).	U.S.A.	M–F	301 All patients of Thoracic Clinic at Memorial Hospital who were diagnosed lung cancer, 1950–52.	468 All 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.
Gsell 1954 (138)	Switzerland	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.
Randig 1954 (283)	Germany	M–F	448 Lung cancer patients in a number of West Berlin hospitals, 1952–1954.	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.
Stocks and Campbell 1955 (337).	(Preliminary: see 1957 report below.)				
Wynder et al., 1956 (375)	U.S.A.	F	105 Patients with lung cancer in several New York City hospitals, 1953–55.	1,304 Patients at Memorial Center with tumors of sites other than respiratory or upper alimentary, 1953–1955.	Cases: Personal interview or questionnaire mailed to close relatives or friends Controls: Personal interview.
Segi et al., 1957 (316)	Japan	M–F	207 Patients with lung cancer in 33 hospitals in all parts of the country, 1953–55.	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 (238)	U.S.A.	M–F	578 Residents of defined areas dying of respiratory cancer, 1947–55.	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 (335)	England	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 or from relatives by health visitors. Controls: Personal interview in hospital.

TABLE 2.—*Outline of methods used in retrospective studies of smoking in relation to lung cancer*—Continued

Investigator, year, and reference	Country	Sex of cases	Number of persons and method of selection		Collection of data
			Cases	Controls	
Schwartz and Denoix 1957 (233).	France	M	608 Patients with bronchopulmonary cancer in hospitals in Paris and a few other cities.	1,204; 2 groups: patients in same hospitals with other cancer, with non-cancer 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.
Hammond et al., 1958 (130)	U.S.A.	F	188 Lung cancer patients available for interview in 20 hospitals, 1955–57.	389 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.
Levin and Goldstein 1958 (222).	U.S.A.	M	400 Men dying of lung cancer, microscopically confirmed, 1952–53.	4,298 Controls in 7 groups including volunteers, hospital and clinic patients, random population sample, and house-to-house survey samples.	Personal interviews by trained workers.
Peras 1959 (227)	Finland	M–F	1,938 Respiratory cancer patients in 4 hospitals and from cancer registry between 1944 and 1953.	1,772 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.
Hammond et al., 1962 (147)	U.S.A.	M	2,101 Sample of 10 percent of white male lung cancer deaths in the U.S. in 1959.	31,516 Random sample from Current Population Survey used to estimate population base.	Cases: By mail from certifying physicians and family informants. Population: Personal interview by Census enumerators.
Lancaster 1962 (199)	Australia	M	289 Hospital patients with lung cancer	476 Two groups, one with other cancer, one with some other disease, matched by sex and age.	Personal interviews of both cases and controls in hospitals.
Hammond and Theuber 1963 [1] (152).	U.S.A.	F	749 Sample of 10 percent of white female lung cancer deaths in the U.S. in 1958 and 1959.	24,720 Random sample from Current Population Survey used to estimate population base.	Cases: By mail from certifying physicians and family informants. Population: Personal interview by Census enumerators.

[1] To be published.

Germane to this concordance is a recent study (386) of Seventh Day Adventists, a religious group in which smoking and alcohol consumption are uncommon. On the basis of expectancy of male lung cancer incidence derived from the control population, only 10 percent of the cases expected were actually found among Seventh Day Adventists.

FORM OF TOBACCO USE

In considering the details of the individual retrospective studies listed in Tables 2 and 3, 13 of the studies, combining all forms of tobacco consumption, found a significant association between smoking of any type and lung cancer (138, 199, 211, 250, 277, 280, 283, 309, 316, 363, 365, 379, 381); 16 studies yielded an even stronger association with cigarettes alone as compared to pipe and/or cigar smoking (38, 82, 147, 192, 207, 222, 236, 237, 238, 277, 283, 301, 311, 314, 335, 379) when these forms of smoking were considered separately and in combinations for males. The females, in the studies investigating the relationship of smoking and lung cancer among them, were almost invariably cigarette smokers so that comparisons with other forms of tobacco use were not indicated.

AMOUNT SMOKED

Twenty-six of the studies quantitated the amount of smoking per day either by combining weights of tobacco consumed in any form, or, more often, by quantities of the specific forms of tobacco. In each of the studies investigating male lung cancer, the degree of association increased as the amount of smoking increased (38, 82, 138, 147, 150, 192, 199, 211, 222, 236, 250, 277, 280, 283, 301, 309, 311, 314, 316, 335, 363, 365, 379, 381). One retrospective study (82) by Doll and Hill found a sharper difference in amount smoked between cases and controls among recent smokers (10 years preceding onset of the disease) than in a comparison of the maximum amount ever smoked. The authors cautioned against accepting this finding as being against their hypothesis of a gradient of risk (which would more properly be tested by the whole life history of "exposure to risk") by citing the inaccuracies resulting from "requiring the patient to remember habits of many years past."

Of the 11 retrospective studies with data on females and tobacco use by amount smoked daily, six (211, 236, 277, 283, 365, 381) showed trends of increasing association with amount smoked daily, but had too few cases for reliability of the trend. However, five studies (82, 150, 152, 335, 375) did have large numbers of female lung cancer cases for analysis by smoking class; three of these (150, 152, 375) were directed towards female cases only. In each of these latter five studies, the degree of association increased with the amount of cigarettes smoked daily.

Four of the retrospective studies dealt with *ex-smokers* as well (147, 152, 211, 314); in one of these (314), where relative risks were derived indirectly by the Cornfield method (61), and in another by conventional use of standardized mortality ratios (147), male ex-smokers showed a lower risk than

TABLE 3.—*Group characteristics in retrospective studies on lung cancer and tobacco use*

Authors	Reference	Year	Males						Females						Remarks
			Cases			Controls			Cases			Controls			
			Number	Percent non-smokers	Percent heavy smokers[1]	Number	Percent non-smokers	Percent heavy smokers[1]	Number	Percent non-smokers	Percent heavy smokers[1]	Number	Percent non-smokers	Percent heavy smokers[1]	
Müller	(250)	1939	86	2.3	68.1	86	16.3	36.0	3	3	3	3	3	3	16 female cases not analyzed.
Schairer & Schöniger	(259)	1943	65	3.2	21.2	270	15.9	9.3	3	3	3	3	3	3	
Potter & Tully	(260)	1945	43	7.0	30.2	1,847	28.0	23.0	3	3	3	3	3	3	Percentages estimated from chart.
Wynder	(268)	1948	134	4.5	54.5	100	19.2	19.2	3	3	3	3	3	3	
Schrek et al.	(211)	1950	82	14.6	18.3	822	22.9	9.2	3	3	3	3	3	3	
Mills & Porter	(267)	1950	444	7.2	3	450	30.5	3	3	3	3	3	3	3	Quantity smoked not considered.
Levin et al.	(267)	1950	296	15.3	3	601	21.7	3	3	3	3	3	3	3	
Wynder & Graham	(281)	1950	605	1.3	51.2	780	14.6	19.1	40	57.5	25.0	552	78.6	1.2	
McConnell et al.	(256)	1952	96	5.4	38.5	196	6.5	23.2	7	57.1	3	14	78.6	3	
Doll & Hill	(30)	1952	1,357	0.5	25.1	1,357	4.5	13.4	105	37.0	11.1	105	54.6	0.9	Percentage "heavy" smokers understated.
Sadowsky et al.	(201)	1953	477	2.5	3	615	13.2	3	3	3	3	3	3	3	Gradient with amount smoked.
Wynder & Cornfield	(279)	1953	96	4.1	67.6	123	20.6	22.3	3	3	3	3	3	3	
Kreyberg	(152)	1953	312	0.6	58.9	300	13.0	25.0	3	3	3	3	3	3	
Lilienfeld	(211)	1953	224	1.8	38.8	1,000	16.0	4.8	22	54.0	4.5	1,002	80.4	0.1	
Brunlow et al.	(36)	1954	829	3.7	74.1	819	10.3	42.7	3	3	3	3	3	3	Data include 498 males, 25 females.
Watson & Cuyler	(285)	1954	286	1.9	71.7	267	9.7	51.6	36	38.3	2.8	181	82.0	1.1	
Nash	(179)	1954	126	0.7	68.1	125	16.0	14.0	3	3	3	3	3	3	
Reading	(269)	1954	415	1.2	34.2	261	5.4	17.9	23	51.5	3.0	131	70.3	0	
Hooton & Campbell	(247)	1955	(Two references (250) below)												
Wynder et al.	(272)	1955	3	3	3	3	3	3	105	38.2	14.2	1,304	66.0	3.4	
Hagi et al.	(216)	1957	169	3	3	2,124	3	3	3	3	3	3	3	3	Quantities smoked stated as averages only. Differences are statistically significant.
Mills & Porter	(258)	1957	494	5.4	28.0	2,888	27.6	5.3	94	53.0	4.3	1,722	73.3	0.5	Percent "heavy" smokers understated. Only 50% survey response among female cases.
Rosin	(253)	1957	2,101	1.9	28.2	3,980	8.7	22.3	255	57.6	17.2	3,402	68.6	10.7	
Schwartz & Denoix	(213)	1957	932	1	58.2	1,206	9.5	36.2	3	3	3	3	3	3	
Hammond et al.	(109)	1958	3	3	3	3	3	3	188	51.6	14.6	339	69.6	8.2	

Lombard & Sangiorgi	(2220)	1959	509	1.6	(**)	4,228	11.0	(**)	(*)	(*)	(*)	(*)	(*)	(*)	Authors' calculations for heavy smoking based on lifetime number of packs of cigarettes.
Ferm	(277)	1960	1,477	6.6	34.5	712	37.2	20.5	129	85.3	26.4	1,060	91.6	0.7	Quantities given only in grams per day.
Hammond et al	(147)	1962	2,191	3.4	41.9	(*)	16.2	12.0	(*)	(*)	(*)	(*)	(*)	(*)	Population sample of 31,616 used as base. Not a case-control study.
Lancaster	(199)	1962	239	2.5	88.1	476	20.1	71.2	(*)	(*)	(*)	(*)	(*)	(*)	
Hammond & Tarnber	(152)	[b]1963	(*)	(*)	(*)	(*)	(*)	(*)	749	60.9	11.5	(*)	67.3	2.5	Population sample of 34,339 used as base. Not a case-control study.

[a] For this table heavy smokers are defined as those smoking 20 or more cigarettes per day.
[b] To be published.
[*] Does not apply.
[**] Data not given.

current smokers but greater than non-smokers. In a third study (152) of lung cancer in women, the ex-smoker risk was lower than the current-smoker risk but approximately equal to that for the non-smoker.

DURATION OF SMOKING

Duration of smoking was considered in 12 of the retrospective studies (82, 150, 207, 222, 236, 283, 301, 311, 316, 335, 375, 381). In only six of them, however, were the data treated in such a way as to permit evaluation of the relationship between duration of smoking and lung cancer—two studies in males (207, 301); two in males and females (82, 236); and two in females only (150, 375). Among the studies of male lung cancer, Levin (207), correcting his data for age, found a relationship between the number of years of cigarette smoking and lung cancer. McConnell (236) found a significant difference in duration of smoking between cases and controls, but was reluctant to draw any definite conclusions. On the other hand, Doll and Hill (82), in their age- and sex-matched study, showed a distinct and statistically significant association between the duration of smoking among males. In a well-conceived analytic study, Sadowsky et al. (301), recognizing that duration of smoking is a function of age, controlled the age variable, and found an increasing prevalence rate of lung cancer with an increase in duration of smoking among all age groups (age at diagnosis).

Among the studies including data on female lung cancer, McConnell had too few female cases to resolve the question of duration of smoking (236) and Doll and Hill, though finding differences between cases and controls, could not establish statistical significance (82). In the two investigations in which only female lung cancer cases were studied (150, 375), neither showed an independent association between duration of smoking and lung cancer. Haenszel states, however, that "among women, the association of starting age and duration of tobacco use with current rate is so strong that it may be unrealistic to expect to find a separate duration effect in retrospective studies of limited size" (150).

AGE STARTED SMOKING

Closely related to duration of smoking and thus pertinent to the length of time that subjects have been exposed to tobacco smoke is the variable of age when smoking was started. Relatively few of the retrospective studies have dealt with this variable. Koulumies (192) found that males with lung cancer had started smoking significantly earlier in life. In fact, 143 of his 845 cases or 17 percent began to smoke below 10 years of age as compared to 6.5 percent among his matched controls. The study of male cases and controls by Breslow et al. (38) found a definite trend in the same direction. Pernu (277) found a statistically significant difference in age at start of smoking, with a higher proportion of the male lung cancer group starting at under 15 years of age. Lancaster (199) indicated that the male lung cancer patients began to smoke at a significantly younger age. One other study (283) showed no difference.

Of the three investigations of female lung cancer which explored this variable, there were too few smokers in one study for a test of significance (277), and in the remaining two (150, 283), no differences were found.

INHALATION

If the association between smoking, particularly cigarette smoking, and lung cancer is a causal relationship, then inhalation should provide more exposure than non-inhalation and should thus contribute significantly to the lung cancer load. Four retrospective investigations were addressed to this question. In the earlier Doll and Hill study (82), no difference in the proportion of smokers inhaling was found among male and female cases and controls. However, four subsequent studies of men (38, 211, 222, 313) found inhalation of cigarettes significantly associated with lung cancer. Although in Breslow's study (38) of age-, sex- and race-matched case and control patients, the variable "quantity-smoked" was not held constant in the comparison when type of smoking though not quantity was controlled, an association was found between inhalation and lung cancer. In the study by Schwartz and Denoix (313) who held constant both type of smoking and amount of cigarettes smoked, the relationship of inhalation was significant for those smoking cigarettes alone but not for the smokers of both cigarettes and pipes. Furthermore, although inhalers among lung cancer patients averaged a significantly higher number of cigarettes per day than did the controls, the relative risk differences between inhalers and non-inhalers, calculated by the Cornfield method (61), become smaller and almost equal each other at the highest cigarette consumption levels. Lombard and Snegireff (222) demonstrated similar relative risk ratios.

HISTOLOGIC TYPE

The earliest retrospective study which considered histologic type of lung cancer was by Wynder and Graham (381) in 1950. These authors presented data on smoking habits of male and female adenocarcinomatous patients and for female patients with epidermoid cancers which were but 25 in number. With this partial analysis only a hint of a higher proportion of smokers among female epidermoid cases could be derived. Of the 1,465 lung cancers in the Doll and Hill retrospective study (82), 995 were histologically confirmed (916 males and 79 females). Of the confirmed cases, 85 percent of the males and 71 percent of the females were of the epidermoid or anaplastic types. Although no statistically significant difference in smoking habits was elicited for the several types, a relatively higher proportion of non-smokers and light smokers were found among patients of both sexes with adenocarcinoma.

Following the presentation by Kreyberg of a Typing Classification of the epidermoid and oat cell or anaplastic types as Group I and the adenocarcinoma and bronchiolar or alveolar cell types as Group II, and the suggestion of a relationship between Group I and smoking (196), several ensuing retrospective studies dealt with this question.

Breslow's study revealed a higher percentage of non-smokers among the patients with adenocarcinoma than among those with epidermoid types (38). In rapid succession six additional retrospective studies analyzed the relationship between histologic type of lung cancer and smoking. The 1956 study of female lung cancers by Wynder et al. (375) indicated that adenocarcinomata apparently had little or no relationship to smoking but that a relationship did exist between smoking and the epidermoid and anaplastic types. Schwartz et al. (313), similarly, in 1957, found a highly significant

association between smoking of cigarettes, amount of smoking as well as inhaling, and the epidermoid and anaplastic types of tumors. No such association with "type cylindrique" was noted. In that same year Doll and Hill furnished Kreyberg with lung cancer slides from 933 British patients. Kreyberg, without knowledge of the patients' smoking history or clinical data, separated these into two groups. A strong correlation was found between smoking history and histologic type; smoking and amount were highly associated with the epidermoid and anaplastic types, and non-smokers were predominantly among the adenocarcinomatous types (86).

In this study of lung cancer in women, Haenszel, et al. (150) found statistically significant relative risk gradients for amount of cigarette smoking among Group I cancer patients. No increased risk was established for Group II cancers. In his later study of a current mortality sample of white males for 1958, Haenszel found relative risk gradients for the several smoking classes for both adenocarcinomas and epidermoid cancers (147). A parallel study of white females for the current mortality sample of 1958 and 1959 showed essentially the same findings, except possibly for a lower effect on adenocarcinomas among smokers of less than one pack daily (152).

Haenszel points out that in both these studies a "true differential in risks" for the two histologic types could well have been diluted seriously by reporting and classification errors which were definitely known to exist from reinquiry of a sub-sample of deaths (152). (For current evaluation, see section on Typing of Lung Tumors.)

RELATIVE RISK RATIOS FROM RETROSPECTIVE STUDIES

Retrospective studies are usually designed to establish the probability of association of an attribute A with disease X; or, given disease X, what is the probability that A will be found in association (P {A|X})? Procedurally, one compares a supposedly representative group of patients with disease X, with another group as controls, in regard to the percentages of individuals with and without the attribute A. This procedure may reveal significant differences leading to judgments of association but it does not yield an estimate of the magnitude of the relative risk of disease X among those with attribute A and those without. A method which estimates this relative risk, developed by Cornfield (61), has been referred to several times earlier and can be applied to data derived from retrospective studies if two assumptions, inherent in the first procedure of judging the association, are made: (a) that patients with disease X interviewed or otherwise studied are a representative sample of all cases with disease X, and (b) that the controls without disease X or who have escaped disease X are a representative sample of all persons without disease X. An estimate of the prevalence of disease X in the population is a requisite.

Such an approach was utilized by a number of investigators in retrospective studies on lung cancer. Doll and Hill (82) made similar calculations and found a linear gradient of deaths from lung cancer for men and women increasing with amount of tobacco smoked daily. Sadowsky et al. (301) found similar increases in risk for amount smoked daily in virtually all but the oldest age groups and calculated an age-standardized risk ratio of 4.6:1 for all smokers compared to non-smokers. These authors also

utilized the data of Wynder and Graham (381) and Doll and Hill (82) for calculating similar risk ratios, deriving ratios of 13.6:1 and 13.8:1, respectively. Their calculations of estimated prevalences by quantity smoked daily for age groupings similar to their own also showed linear increases of risk.

Breslow et al. (38) treated their retrospective data similarly and developed relative risk ratios of 7.7:1 for males aged 50–59 years and 4.6:1 for those aged 60–69. In considering heavy smokers (40 or more cigarettes per day), they showed relative risk ratios of 17:1 and 25.5:1, respectively. Randig (283) also demonstrated a linear progression of risk with increasing amounts of daily tobacco consumption and an over-all ratio of 5.1:1 for all smokers to non-smokers among males and 2.2:1 for females. Schwartz and Denoix (313) reported similar findings in amount smoked daily and a risk ratio of smokers to non-smokers of approximately 8:1. Lombard and Snegireff (222) approached their data in a different way, utilizing "lifetime number of packs of cigarettes consumed" as a measure of exposure. Their estimated prevalence rates also increase linearly with amount smoked. The risk ratio which can be calculated from their tabulated data ranges from 2.4:1 for light smokers to 34.1:1 for heaviest smokers.

Haenszel, in his two studies on male and female lung cancer mortality as related to residence and smoking histories, calculated relative risk ratios of 4.1:1 for one pack or less daily and 16.6:1 for more than one pack a day among males (147), and 2.5:1 and 10.8:1, respectively, among females (152). Table 4 summarizes the relative risk findings of the nine studies.

TABLE 4.—*Relative risks of lung cancer for smokers from retrospective studies*

Author and Reference	Year	Sex	Relative risk—Smokers: non-smokers
Sadowsky et al. (301)	1953	M	4.6
Doll and Hill (82)	1952	M	13.8
Wynder and Graham (381)	1950[1]	M	13.6
Breslow et al. (38)	1954	M	7.7 age 50–59 4.6 " 60–69 17.0 " 50–59 } very heavy smokers 25.5 " 60–69 }
Randig (283)	1954	M-F	5.1 M 2.2 F
Schwartz and Denoix (313)	1957	M	8.0
Lombard and Snegireff (222)	1959	M	2.4 light smokers 34.1 heavy smokers
Haenszel (147)	1962	M	4.1 <1 pack/day 16.6 >1 pack/day
Haenszel (152)	Unpublished	F	2.5 <1 pack/day 10.8 >1 pack/day

[1] Calculated by Sadowsky et al. (301) from other authors' data.

Prospective Studies

It has been pointed out that in retrospective studies the usual approach is to determine the frequency of an attribute among cases and controls. This measure does not provide estimates of the risks of developing the disease

among individuals with and without the attribute unless one makes assumptions referred to above. The validity of such assumptions may at times be suspect, for the cases may not be representative of the total population with the disease nor the controls representative of the population without the disease. Thus, some retrospective studies may not truly assess the existent risks with reasonable accuracy. However, when *all* the cases of a disease in an area and a representative sample of the population without the disease are included in a study, the estimates of risk bear high validity.

Despite the criticisms leveled at the retrospective method in general and its obvious defects as practiced by some investigators, a number of the retrospective studies on lung cancer have indeed overcome most of the criticisms of major import leveled at the method. These criticisms and their implications will be treated specifically below in the section on an Evaluation of the Association Between Smoking and Lung Cancer. Suffice it to say at this point that certain shortcomings of the retrospective survey approach, some real and some exaggerated, led several courageous investigators to undertake the necessarily protracted, expensive, and difficult prospective approach.

The first prospective study encompassing total and cause-specific mortality in a human population was initiated in October 1951 among British physicians by Doll and Hill (83, 84). There then followed in rather rapid succession, five additional independent studies in the United States and Canada (25, 87, 88, 96, 97, 157, 162, 163), all but one of which continue to be active. The earlier study, by Hammond and Horn, among 187,783 white males aged 50–69 years, initiated between January and May 1952, was terminated after 44 months of follow-up (162, 163). This has been succeeded by the current Hammond study which broadened its age-base (35–89 years) and contains 1,085,000 persons (in 25 states) of whom 447,831 are males (157).

These studies have been described in detail, analyzed, and evaluated in Chapter 8 of this Report where a discussion of differences in total mortality between smokers and non-smokers has been presented, and are summarized in Table 1 of that chapter. All the prospective studies thus far have shown a remarkable consistency in the significantly elevated mortality ratios of smokers particularly among the "cigarettes only" smoking class. Of special interest is the fact that in a number of the studies the magnitude of the association between cigarette smoking and total death rates has increased as the studies have progressed. This has particularly been true for lung cancer. The presently calculated total mortality ratios have been presented in Table 2 of Chapter 8 of this Report.

With reference to the smoking and lung cancer relationship, each of the seven prospective studies has thus far revealed an impressively high lung cancer mortality ratio for smokers to non-smokers. Examination of Table 5, which presents in summary form the lung cancer mortality ratios for the seven studies by smoking type and amount, derived both from the published reports of these studies and current information from the investigators wherever available, reveals a range of ratios from 6.0 to 25.2 with a median value of 10.7 for all smokers irrespective of type or amount. For smokers currently using cigarettes only at the time of enrollment in the studies, the ratios range from 4.9 to 20.2 with a mean value of 10.4 as derived from a summation of observed and expected values of most recent data.

Several of the studies have fortunately provided data for a measure of the "dose of exposure" relationship (84, 88, 96, 157, 163). It can readily be seen from Table 5 that the mortality ratios increase progressively with amount of smoking. The pivot level appears to be 20 cigarettes per day. Cigar and/or pipe smokers (to the exclusion of cigarettes) manifest ratios lower than any of the cigarette smoking classes, including combinations of cigarettes with pipes and/or cigars (25, 84, 88, 157, 163). One study provided data on occasional smokers (163). These have a ratio very close to that of non-smokers. Ex-smokers of cigarettes (83, 88, 163) fall into levels of risk ratios below those for current smokers of cigarettes depending upon the length of the interval since smoking was stopped. In the Doll and Hill study (83), the ex-smoker ratio was less than the current smoker ratio even when cessation had occurred less than 10 years before entry into the study. This, however, was not true for the first Hammond and Horn study (163). In this latter study, if smoking had ceased more than 10 years before entry, the lung cancer mortality ratios were lower than for current smokers at the corresponding daily consumption levels, but if cessation of smoking had occurred less than 10 years before entry, the ratios were virtually identical to those for current cigarette smokers at the corresponding daily consumption levels. The Dorn material (87, 88), currently brought up to date (89), provides a measure of relative risk by amounts of smoking prior to stopping. The ratios thus elicited are again below those for current cigarette smokers of corresponding daily amounts.

At this time it is difficult to assess the effect of other variables such as duration of smoking and starting age on lung cancer mortality since cross-classification by these variables, and amount smoked as well, leads to cells with small numbers of deaths. Most prospective studies have thus far confined themselves to analyzing the effect of these additional variables on deaths from all causes, or in one case (157) from cardiovascular diseases. The current Hammond study is concerned with inhalation practices, but here also the total number of lung cancer deaths analyzed to date does not permit extensive classification by age, type of smoking, amount smoked daily, present smoking status, and age when smoking was begun. In the studies of total mortality ratios, duration of smoking, obviously immediately dependent upon the age of the individual, was in turn dependent upon age when smoking (cigarettes) was begun. Age when smoking began was also a determinant, not only of the number of cigarettes smoked daily, but of the degree of inhalation, with smokers starting at earlier ages very distinctly tending to smoke more and inhale more deeply than those starting to smoke at older ages (157). According to Hammond, men who smoke more per day also tended to inhale more deeply than those who smoke fewer cigarettes per day. When inhalation and quantity smoked were held constant, the total mortality ratios also increased as age at start of smoking decreased.

The stability of the lung cancer mortality ratios referred to in Table 5 is to a great extent dependent upon the number of observed lung cancer deaths among non-smokers from which the expected values for the several smoker classes are calculated. Referring again to Table 5, in at least two of the studies (83, 96), calculation of the expected deaths among smoker classes had to be based on extremely small numbers of non-smokers. However,

TABLE 5.—*Mortality ratios for lung cancer by smoking status, type of smoking, and amount smoked, from seven prospective studies*

Study	Doll and Hill	Hammond and Horn	Dorn	Dunn, Linder and Breslow—Occupational	Dunn, Buell and Breslow—Legion	Best, Jones and Walker	Hammond
Lung cancer deaths in Study	129	448	535	129	98	221	414
Lung cancer deaths Non-smokers	†3	†25	†66	†3	†12	†8	†16
(Reference number)	(38)	(169)	(38)	(96)	(97)	(25)	(157)
MORTALITY RATIOS:							
All Smokers	12.8	10.7	6.0	–	–	*25.2	†8.1
1–14 gm. tobacco	6.7	–	–	–	–	–	–
15–24 gm. tobacco	12.3	–	–	–	–	–	–
25 gm. tobacco	23.7	–	–	–	–	–	–
Current: **							
Cigarettes only	†20.2	†10.0	†12.0	†15.9	†4.9	†11.7	†9.6
<10	4.4	†5.8	†5.2	(5)– 8.3	–	†8.4	–
10–20	10.8	†7.3	†9.4	(10)– 9.0	–	†13.5	–
21–39	42.7	†15.9	†13.1	(20)–19.4	–	†15.1	–
40+		†23.7	†23.3	(30)–25.1	–		–
				(40)–28.7			
≤1 pack †	8.1	6.9	8.1	13.6	4.2	11.8	–
>1 pack †	45.8	16.9	18.0	24.1	7.4	15.1	–
Pipes only	5.4	2.6	1.2	–	–	†1.1	†1.5
Cigars only	†4.6	1.0 †1.3	1.5 †1.6	–	–		
Pipes and cigars		–	–	–	–		
Cigarettes, pipes and cigars	9.7	10.7	6.2	–	–	†24.4	–
Occasional	–	1.2	–	–	–	–	–
Ex-Smokers:							
>10 yrs. since stopped	5.0	–	–	–	–	–	–
<20 cigarettes	–	2.4	–	–	–	–	–
>20 cigarettes	–	17.5	–	–	–	–	–
<10 yrs. since stopped	5.4	–	–	–	–	–	–
<20 cigarettes	–	10.4	–	–	–	–	–
>20 cigarettes	–	22.5	–	–	–	–	–
<20 cigarettes (irrespective of when stopped)	–	–	†1.3	–	–	–	–
>20 cigarettes (irrespective of when stopped)	–	–	†1.6	–	–	–	–

*Current and ex-smokers combined.
†Most recent information.
–Data not available or not available for designated classes.
**Two California studies and current Hammond study include all cigarette smokers (cigarettes and other and current and ex-cigarette smokers).

the other studies have now yielded significantly greater numbers of non-smoker lung cancer deaths and in at least three of them (88, 157, 163) these are now appreciable.

Experimental Pulmonary Carcinogenesis

ATTEMPTS TO INDUCE LUNG CANCER WITH TOBACCO AND TOBACCO SMOKE

Few attempts have been made to produce bronchogenic carcinoma in experimental animals with tobacco extracts, smoke, or smoke condensates. With one possible exception (289), none has been successful (331).

Mice rarely develop spontaneous bronchogenic, oral, esophageal, gastric, prostatic, laryngeal, or vesical carcinomas, but certain inbred strains have a high incidence of spontaneous pulmonary adenomas (6). The administration, by any route, of carcinogenic polycyclic hydrocarbons, including some found in tobacco tar, increases the incidence and decreases the time of occurrence of pulmonary adenomas. These tumors are usually regarded as benign, and probably arise from the alveolar epithelium (4, 5, 6, 131, 330) rather than the bronchial wall. They have no resemblance to most human bronchogenic carcinomas.

Essenberg (106) and Mühlbock (248) exposed mice to cigarette smoke, but their reported results are equivocal. Lorenz et al. (224) and Leuchtenberger et al. (206) did not observe an increase in pulmonary adenomas in mice that inhaled cigarette smoke.

Leuchtenberger et al. (205a.) described a sequence of microscopic changes in lungs of mice exposed to cigarette smoke resembling somewhat those found by Auerbach et al. in the lungs of human smokers. No dose-response effect was reported. The morphologic findings consisted of bronchitis with proliferation of the epithelium. Some areas of hyperplasia showed atypical changes. However, the changes were reversible when exposure to smoke was stopped. The production of bronchogenic carcinomas has not been reported by any investigator exposing experimental animals to tobacco smoke.

Most experiments in which tobacco tars were brought into direct contact with the lung and tracheobronchial tree of experimental animals have yielded negative results (273, 274, 275). Blacklock (29) found one carcinoma when tar from cigarette filters was placed in olive oil together with killed tubercle bacilli and injected into the hilum of a small number of rats. Rockey et al. (289) painted tobacco tar three to five times each week on the trachea of dogs with a tracheocutaneous fistula. Hyperplastic changes with squamous metaplasia of the bronchial epithelium were seen in seven dogs that survived 178 to 320 days. Carcinoma-in-situ was reported to occur in three, and invasive carcinoma in one out of 137 dogs, but this work has not yet been confirmed.

SUMMARY.—Bronchogenic carcinoma has not been produced by the application of tobacco extracts, smoke, or condensates to the lung or the tracheobronchial tree of experimental animals with the possible exception of dogs.

SUSCEPTIBILITY OF LUNG OF LABORATORY ANIMALS TO CARCINOGENS

POLYCYCLIC AROMATIC HYDROCARBONS.—Epidermoid carcinoma has been induced in mice by Andervont by the transfixion of the lungs or bronchi with a thread coated with a carcinogen (5) and by Kotin and Wiseley (191) by treatment with an aerosol of ozonized gasoline plus mouse-adapted influenza viruses.

Kuschner et al. (197, 197a) induced epidermoid carcinomas in the lungs of rats by the local application of polycyclic aromatic hydrocarbons, either by thread transfixation or pellet implantation. Distant metastases occurred from some of the carcinomas. The changes in the bronchial tree at different times prior to the appearance of cancer included hyperplasia, metaplasia and anaplasia of the surface epithelium as well as of the subjacent glands. These changes resembled those described by Auerbach in the tracheobronchial tree of human smokers (9).

Stanton and Blackwell (324) induced epidermoid carcinoma in the lungs of rats that had received 3-methylcholanthrene intravenously. The carcinogen was deposited in areas of pulmonary infarction.

Saffiotti et al. (302) produced squamous cell bronchogenic carcinomas in hamsters by weekly intubation and insufflation of benzo(a)pyrene (4 percent) ground with iron oxide (96 percent) resulting in a dust with particles smaller than 1.0 micron. A proliferative response followed by metaplasia preceded the appearance of the carcinomas, but was not an invariable antecedent.

VIRUSES.—Bronchogenic carcinoma has been induced in animals inoculated with polyoma virus by Rabson et al. (282). Carcinogens enhance the effect of viruses known to cause cancer in animals (99) and localize the neoplastic lesions at the site of inoculation of the virus (98). However, no evidence has been forthcoming to date implicating a virus in the etiology of cancer in man.

POSSIBLE INDUSTRIAL CARCINOGENS.—Vorwald reported that exposure of rats to beryllium sulfate aerosol resulted in carcinomas of the lung; [illegible] percent were epidermoid but most were adenocarcinomas. The tumors usually arose from the alveolar or bronchiolar epithelium. He also produced bronchogenic carcinomas in two out of ten rhesus monkeys injected with beryllium oxide and in three out of ten exposed to beryllium oxide by inhalation (357).

Lisco and Finkel in 1949 (217) reported the production of epidermoid cancer of the lung in rats with radioactive cerium. Subsequently many other investigators have succeeded in producing carcinomas of the lung, predominantly of the epidermoid type, in a high percentage of rats and mice with other radioactive substances. The various modes of exposure included inhalation, intratracheal injection, or insufflation and implantation of wire or cylinder. These experiments were reviewed by Gates and Warren in 1961 (125).

Hueper exposed rats and guinea pigs to nickel dust and found metaplastic and anaplastic changes in the bronchi (180). Following up earlier work in which squamous metaplasia of the bronchial epithelium was found in rats exposed to nickel carbonyl (341), Sunderman and Sunderman (3[illegible]) induced bronchogenic carcinoma in rats by exposure to this compound. This

group also found 1.59 to 3.07 μg. of nickel per cigarette in the ash and in the smoke in several different brands. About three-fourths was contained in the ash. Although Hueper and Payne (182, 183) and Payne (270) have demonstrated that pure chromium compounds will produce both sarcomas and carcinomas in several tissues in rats and mice, bronchogenic carcinomas have not been produced by inhalation of chromium compounds in experimental animals. Experiments designed to test the carcinogenicity of arsenical compounds have been either negative or inconclusive.

Asbestosis can be produced without difficulty in experimental animals by inhalation of asbestos fibers (359), but efforts to produce bronchogenic carcinoma have been unsuccessful (129, 181, 227, 358).

SUMMARY.—The lungs of mice, rats, hamsters, and primates have been found to be susceptible to the induction of bronchogenic carcinoma by the administration of polycyclic aromatic hydrocarbons, certain metals, radioactive substances, and oncogenic viruses. The histopathologic characteristics of the tumors produced are similar to those observed in man and are frequently of the squamous variety.

ROLE OF GENETIC FACTORS IN PULMONARY ADENOMAS IN MICE

Genetic factors exert a determining influence on the spontaneous development and induction of lung tumors in mice. Early studies of Murphy and Sturm (251) and of Lynch (225, 226) demonstrated the development of pulmonary tumors in mice after the skin was painted with coal tar, and Lynch (225) indicated the existence of genetic factors in the development of these tumors. Later investigations of Heston (169, 170) on the effect of intravenous injection of dibenzanthracene and the studies of several other investigators (3, 4, 27, 47, 320) utilizing different techniques gave additional evidence of the operation of genetic factors in induced tumors. Linkage between multiple genes for susceptibility to spontaneous and induced tumors in mice and specific chromosomes has also been established (47, 168) and transplantation experiments (171, 173) indicate that the genetic susceptibility resides within the pulmonary parenchyma. A number of investigators (36, 47, 124, 131) demonstrated conclusively that these tumors usually arise distal to the bronchus and are probably alveogenic. Metastases rarely occur. The relative importance of genes for susceptibility to these tumors of the lung is indicated by an incidence ranging from a few tumors to over 90 percent, depending on the inbred strain examined.

Spontaneous tumors of the lungs are rare in species of laboratory animals other than mice, and the genetics of these neoplasms in other species has been investigated only superficially.

SUMMARY.—Genetic susceptibility plays a significant role in the development of pulmonary adenomas in mice.

Pathology—Morphology

RELATIONSHIP OF SMOKING TO HISTOPATHOLOGICAL CHANGES IN THE TRACHEOBRONCHIAL TREE

In an extensive and controlled blind study of the tracheobronchial tree of 402 male patients, Auerbach et al. (11, 13, 15) observed that several

kinds of changes of the epithelium were much more common in the trachea and bronchi of cigarette smokers and subjects with lung cancer than of non-smokers and of patients without lung cancer (Table 6). The epithelial changes observed were (a) loss of cilia, (b) basal cell hyperplasia (more than two layers of basal cells), and (c) presence of atypical cells. The atypical cells had hyperchromatic nuclei which varied in size and shape. The arrangement of such cells was frequently disorderly (see illustrations below). Hyperplastic changes were also seen in the bronchial glands.

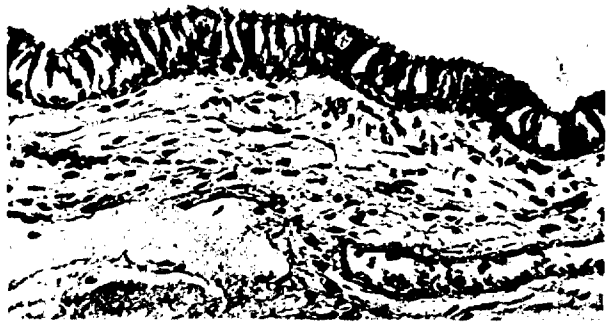
TABLE 6.—*Percent of slides with selected lesions,*[1] *by smoking status and presence of lung cancer*

Group	Number cases	Number slides	Percent of slides with cilia absent and averaging 4 or more cell rows in depth			
			No cells atypical	Some cells atypical	All cells atypical [2]	Total
Cases without lung cancer						
Never smoked regularly	65	3,324	1.0	0.03	.....	1.1
Ex-cigarette smokers	72	3,436	3.5	0.4	0.2	4.1
Cigarettes—½ pk. a day	36	1,824	0.2	4.2	0.3	4.7
Cigarettes—½-1 pk. a day	59	3,016	.....	7.1	0.8	7.9
Cigarettes—1-2 pks. a day	143	7,062	.....	12.6	4.3	16.9
Cigarettes—2+ pks. a day	36	1,787	.....	26.2	11.4	37.5
Lung cancer cases [3]	63	2,784	.....	12.5	14.3	26.8

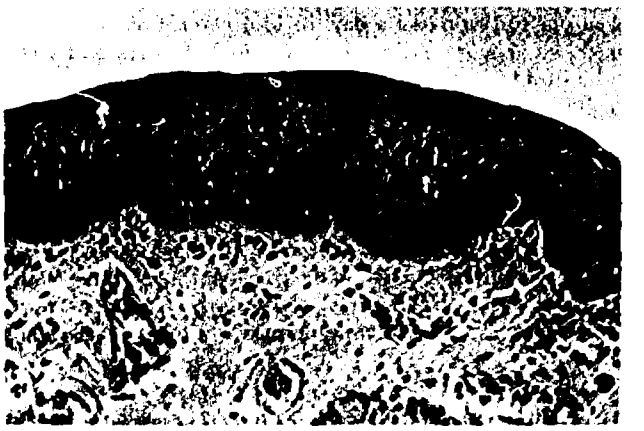
[1] In some sections, two or more lesions were found. In such instances, all of the lesions were counted and are included in both individual columns and in the total column of the table. Lesions found at the edge of an ulcer were excluded.
[2] These lesions may be called carcinoma-in-situ.
[3] Of the 63 who died of lung cancer, 55 regularly smoked cigarettes up to the time of diagnosis, 5 regularly smoked cigarettes but stopped before diagnosis, 1 smoked cigars, 1 smoked pipe and cigars, 1 was an occasional cigar smoker.

Each of the three kinds of epithelial changes was found to increase with the number of cigarettes smoked (Table 6). In smokers who had no cancers, frequency and intensity of these changes correlated with the number of

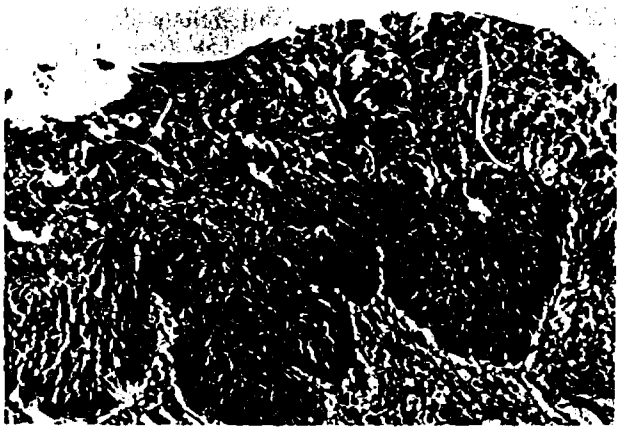
EXAMPLES OF NORMAL AND ABNORMAL BRONCHIAL EPITHELIUM



1. *Normal*



2. *Basal-cell hyperplasia—replacement of ciliary epithelium with a thick layer of cells resembling stratified squamous epithelium.*



3. *Extensive basal-cell hyperplasia with numerous atypical cells.*

Source: Auerbach, Oscar. Special communication to the Surgeon General's Advisory Committee on Smoking and Health.

cigarettes smoked. Among non-smokers, lesions composed entirely of atypical cells with loss of cilia were uniformly absent, although a few could be seen with more than two rows of basal cells containing some atypical cells. In contrast, atypical cells were found in all lesions seen in the tracheobronchial tree of patients who smoked two or more packs of cigarettes a day, irrespective of the presence of hyperplasia and/or cilia loss or whether the patients died of lung cancer. The most severe lesion, aside from invasive carcinoma, consisted of loss of cilia, and hyperplasia up to five or more cell rows composed entirely of atypical cells. This lesion was never found among men who did not smoke regularly and was found only rarely among light smokers. However, it was found in 4.3 percent of sections from men

who smoked one to two packs a day, in 11.4 percent of sections from those who smoked two or more packs a day, and in 14.3 percent of sections from smokers who died of lung cancer (15).

While epithelial changes were found in all portions of the tracheobronchial tree, quantitative differences were found between the changes in the trachea and those in the bronchi; hyperplastic lesions consisting entirely of atypical cells without cilia were found in all regions of the bronchial mucosa but only rarely in the trachea. It is notable that cancer rarely occurs in the trachea.

In 35 children less than 15 years of age, Auerbach et al. (16) found the same percent of epithelial changes in the tracheobronchial tree as in the same number of adults who had never smoked regularly (16.6 percent of children and 16.8 percent of adults). No hyperplasia with atypical cells was seen in any section.

Later, Auerbach et al. (15a.) studied the morphology of the tracheobronchial tree from 302 women and 456 men with respect to additional variables—sex, age, pneumonia, and amount smoked. One or more epithelial lesions were found in 68.2 percent of sections from men smokers and 68.6 percent from women smokers when matched groups were examined. However, on further study, hyperplastic lesions composed entirely of atypical cells were found in 6.9 percent of the sections from the male group and in 2.5 percent of those from females.

Matched groups of male cigarette smokers of two age groups (averages of 37 and 67 years) were compared. Many more lesions, characterized by a large number of cells with atypical nuclei, were observed in the older than in the younger group. In a parallel study of women who did not smoke (average ages of 46 and 76 years), no difference in the number or type of lesions was noted. Few changes in the bronchial epithelium were found in sections from 27 women non-smokers over 85 years of age.

Occasional atypical changes were found in women non-smokers (a) who died of pneumonia, (b) who died of various other causes but had pneumonia at the time of death, and (c) who died with no evidence of pneumonia. However, basal cell hyperplasia, loss of cilia, and ulceration were found more frequently in sections from women who died with pneumonia than from women who had no evidence of pneumonia. These observations are in agreement with those of other investigators who found metaplasia of the bronchial epithelium to be more frequent in patients with various non-neoplastic pulmonary diseases than in controls without such disease (256, 305, 352, 366).

Far fewer epithelial lesions were found in non-smokers than in pipe, cigar, or cigarette smokers (15a.), the difference being particularly evident in the occurrence of atypical cells. However, sections from pipe and cigar smokers showed fewer epithelial lesions than did sections from cigarette smokers. Cells with atypical nuclei were found far more frequently in cigarette smokers than in cigar or pipe smokers (Table 7).

In 72 male ex-cigarette smokers who had smoked for at least ten years and had not smoked for at least five years prior to the time of death, there were less hyperplasia, less loss of cilia, and fewer atypical cells than in sections from current cigarette smokers (14). An interesting by-product of this study was the finding of "cells with disintegrating nuclei" in the

TABLE 7.—*Changes in bronchial epithelium in matched triads of male non-smokers and smokers of different types of tobacco.*[1]

Group	Number of subjects	Total sections with epithelium	Sections with 1 or more epithelial lesions		3+-cell rows with cilia present		Cilia absent		Atypical cells present		Atypical cells present with cilia absent		Entirely atypical cells with cilia absent [2]	
			Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
7th set (none vs. pipe vs. cigarette)[3]														
Non-smokers	20	985	214	21.7	110	11.2	101	10.3	26	2.6	3	0.3	0	----
Pipe smokers	20	924	605	65.5	352	38.1	117	12.7	342	37.0	29	3.1	0	----
Cigarette smokers	20	914	885	96.8	810	88.6	116	12.7	870	95.2	111	12.1	35	3.8
8th set (none vs. pipe vs. cigarette)														
Non-smokers	25	1,246	285	22.9	167	13.4	132	10.6	9	0.7	1	0.1	0	----
Pipe smokers	25	1,164	800	68.7	451	38.7	172	14.8	445	38.2	38	3.3	0	----
Cigarette smokers	25	1,126	1,084	96.3	999	88.7	238	21.1	1,008	89.5	205	18.2	70	6.2
9th set (none vs. cigar vs. cigarette)														
Non-smokers	35	1,706	467	27.4	216	12.7	281	16.5	14	0.8	3	0.2	0	----
Pipe smokers	35	1,733	1,573	90.8	694	40.0	247	14.3	1,275	73.6	173	10.0	5	0.3
Cigarette smokers	35	1,526	1,511	99.0	1,414	92.7	428	28.0	1,493	97.8	417	27.3	196	12.8

[1] Modified table from Auerbach et al. (15a).
[2] Carcinoma in situ.
[3] Triads were matched for age, occupation, residency and (for smokers) by amount of tobacco used.

bronchial epithelium of 43 out of 72 ex-smokers. These cells were not found in the bronchial epithelium of current cigarette smokers or non-smokers. They were considered by Auerbach et al. to be pathognomonic of the ex-smoker.

Many of the histopathologic findings observed by Auerbach et al. in the bronchial epithelium of smokers have been confirmed by other investigators (64, 155, 189, 304).

The significance of the hyperplastic changes in the bronchial epithelium for the pathogenesis of lung cancer in smokers is not fully understood. The establishment of a link between the hyperplastic changes and the subsequent development of lung cancer would relate smoking causally to lung cancer. However, the non-specificity of hyperplasia of the bronchial epithelium is universally recognized. Furthermore, similar changes are known to be reversible.

On the other hand, evidence from both human and experimental observations points strongly to the conclusion that some hyperplastic changes of the bronchial epithelium, especially those with many atypical alterations, are probably premalignant.

It is well documented that the bronchial trees of patients with lung cancer have areas, sometimes very widespread, of epithelial hyperplasia containing many atypical and bizarre cells. This was reported by Lindberg in 1935 (216) and by many other investigators (10, 12, 28, 52, 134, 265, 285, 349, 370). Black and Ackerman (28) have carried out an extensive study of the relationship between metaplasia and anaplasia and lung cancer in human lungs and have presented strong circumstantial evidence for the opinion that the basal cell hyperplasia with advanced atypical changes and loss of cilia (the so-called carcinoma in-situ) represent a stage in the development of lung cancer. They also emphasized, as has Auerbach et al. (12), the frequent occurrence of atypical basal cell hyperplasia at multiple sites in the bronchial tree considerably removed from the site of the lung cancer. They have pointed out the similarities between the atypical hyperplasias in the tracheobronchial tree and carcinoma in-situ in other sites, such as the cervix, skin, and larynx.

Lung cancer was induced in animals by radioactive substances (198, 217), chemical carcinogens (198, 340), and air pollutants plus influenza virus (191). These studies have demonstrated the occurrence of extensive atypical hyperplastic changes in the bronchial epithelium of experimental animals preceding the appearance of lung cancer. The changes described are, on the whole, similar to those seen by Auerbach et al. in the bronchial epithelium of heavy cigarette smokers and by others in patients with lung cancer. The hyperplastic lesions in animals do not invariably develop into cancer. This appears to be the case also in man (14).

In view of these observations, it seems probable that some of the lesions found in the tracheobronchial tree in cigarette smokers are capable of developing into lung cancer. Thus, these lesions may be a link in the pathogenesis of lung cancer in smokers.

SUMMARY.—Several types of epithelial changes are much more common in the trachea and bronchi of cigarette smokers, with or without lung cancer, than of non-smokers and of patients without lung cancer. These epithelial

changes are (a) loss of cilia, (b) basal cell hyperplasia, and (c) appearance of atypical cells with irregular hyperchromatic nuclei. The degree of each of the epithelial changes in general increases with the number of cigarettes smoked. Extensive atypical changes have been seen most frequently in men who smoked two or more packs of cigarettes a day. Hyperplasia without atypical changes was seen in the bronchial tree of children under 15 years of age and in women non-smokers at all ages who died with pneumonia. Women cigarette smokers, in general, have the same epithelial changes as do men smokers. However, at given levels of cigarette use, women appear to show fewer atypical cells than do men. Older men smokers have many more atypical cells than do younger men smokers. Men who smoke pipes or cigars have more epithelial changes than do non-smokers, but have fewer changes than do cigarette smokers consuming approximately the same amount of tobacco. Male ex-cigarette smokers have less hyperplasia and fewer atypical cells than do current cigarette smokers.

CONCLUSION.—It may be concluded on the basis of human and experimental evidence that some of the advanced epithelial hyperplastic lesions with many atypical cells, seen in the bronchi of some cigarette smokers, are probably premalignant.

TYPING OF LUNG TUMORS

Historical aspects of the typing of lung tumors in relation to possible etiological agents are reviewed in the section on Retrospective Studies, Histologic Types.

Kreyberg (195, 196) noted that the increase of lung cancer in recent decades seemed to occur for only certain types of lung cancers (his Group I), and that other types did not increase (his Group II). Kreyberg's classification is compared with the World Health Organization classification in Table 8. His Group I includes epidermoid carcinomas and small-cell anaplastic carcinomas. His Group II includes adenocarcinomas and a few rare types. He postulated that a determination of the ratio between Groups I and II is a good index of the occurrence and magnitude of an increase in lung cancer in a given locality and his epidemiologic studies linked the increase almost entirely to the use of cigarettes. His thesis has been accepted by many while disputed by others.

The results of the study of lung cancer at Los Angeles County General Hospital (LACGH) by Herrman and Crittenden (167) did not confirm Kreyberg's conclusions. These investigators, analyzing the autopsy data on lung cancer from 1927 to 1957 at LACGH, observed a marked increase in the number of lung cancer cases as had been noted by many other investigators. However, the ratio of Kreyberg's Group I to Group II had not changed perceptibly over this period and was notably lower than in other series studied.

The Committee on Smoking and Health sponsored a workshop in which slides from coded cases of lung cancer from four different institutions in three areas of the United States were typed "blind" by Dr. Kreyberg and pathologists from the cooperating institutions.[1] There was good agreement as to typing. The low ratio of Group I to Group II cancers at LACGH was confirmed. When typing of the reviewed cases was compared with smoking

[1] Workshop on typing of lung tumors held in Washington, D.C., April 11, 1963.

TABLE 8.—*Relation between WHO and Kreyberg classifications of lung tumors*

WHO classification [1]	Kreyberg classification [2]
A. *Epithelial Tumors*	
1. Epidermoid carcinomas	Group I
a. highly differentiated	
b. moderately differentiated	
c. slightly differentiated	
2. Small-cell anaplastic carcinomas	Group I
a. with oval-cell structure ("oat-cell" carcinoma)	
3. Adenocarcinomas	Group II
a. acinar (with or without formation of mucus)	
b. papillary (with or without formation of mucus)	
c. tumors with a predominance of "large cells" some of which show formation of glands and/or production of mucus.	
4. Large-cell undifferentiated carcinomas	Other [3]
5. Combined epidermoid and adenocarcinomas	Other
6. Bronchiolo-alveolar cell carcinomas	Group II
7. Carcinoid tumors (solid, trabecular, alveolar)	Group II
8. Tumors of mucous glands	Group II
a. cylindroma	
b. muco-epidermoid tumors	
9. Papillomas of the surface epithelium	Other
a. epidermoid	
b. epidermoid with goblet cells	
B. *Sarcomas*	Other
C. *Combined Tumors of Epithelial and Mesenchymal Cells*	Other
D. *Mesotheliomas of the Pleura*	Other
1. Localized	
2. Diffuse	
E. *Tumors Unclassified*	

[1] Committee on Cancer of the Lung, World Health Organization.
[2] Kreyberg, L. Histological Lung Cancer Types. A Morphological and Biological Correlation. Norwegian Universities Press, 1962.
[3] Types marked "other" are not included in either of Kreyberg groups.

histories, moreover, it became evident that both Group I and Group II were increased among heavy smokers.

Several factors were recognized to influence Group I/Group II ratios: (a) source of material (for example, significant differences in the ratio were found between autopsy and surgical materials, and between surgical materials obtained by biopsy and by resection during operation for lung cancer); (b) failure to autopsy certain cases which were judged to be inoperable (the patient being sent home as incurable); (c) the fact that Group I (squamous and oval-cell) carcinomas are more likely to be among the operable cases and among those accessible to bronchoscopy, and (d) variations in selection of patients in different institutions.

An independent review of the histopathology of 1,146 lung cancer cases from the U.S. veterans study (policyholders) by Dorn, Herrold and Haenszel (Table 9) (89) showed high mortality ratios for both Group I and Group II cancers in current heavy smokers (over 20 cigarettes/day), although Group I had a higher mortality ratio (31.2) than Group II (7.2).

Another study of Haenszel on white females (152), as well as studies of female patients at Massachusetts General Hospital (54), Roswell Park Memorial Institute (133), Presbyterian Hospital (323), and Washington University (260), indicated that adenocarcinoma is also contributing to the increment of lung cancer in women.

CONCLUSIONS—(a) The histological typing of lung cancer is reliable. However, the use of the ratio of Group I and Group II is an index to the magnitude of increase in lung cancer is of limited value.

TABLE 9.—*Mortality ratios for cancer of the lung by smoking class and by type of tumor, U.S. veterans study*

	All Deaths	Group I	Group II
Nonsmokers [1]	1.0	1.0	1.0
Pipe and/or cigar smokers	1.5	2.2	0.6
Cigarette smokers, total [2]	8.2	15.4	5.1
Current			
Total	10.0	18.9	5.8
≤20 cigarettes/day	7.1	12.9	5.1
>20 cigarettes/day	16.0	31.2	7.2
Discontinued (By Maximum Amt. Ever Smoked)			
Total	4.7	8.4	3.7
≤20 cigarettes/day	3.5	6.6	2.7
>20 cigarettes/day	7.4	12.1	5.6

[1] Includes occasional smokers.
[2] Includes men who were using pipe and/or cigars in addition to cigarettes.

Source: Dorn, H. F., Haenszel, W. and Herrold, K. (89) (see Chapter 8 also).

(b) Squamous and oval-cell carcinomas (Group I) comprise the predominant types associated with the increase of lung cancer in both males and females. In several studies, adenocarcinomas (Group II) have also increased in both sexes although to a lesser degree.

Evaluation of the Association between Smoking and Lung Cancer

It is not practical to attempt an experiment in man to test whether a causal relationship exists between smoking of tobacco and lung cancer. Such an experiment would imply the random selection of very young subjects living under environmental conditions as nearly identical as possible, and random selection of those who were to be smokers and those who were to be the non-smoker controls. Their smoking and other habits would need to be held constant for many years. Because of the relatively low incidence of lung cancer in the human population, both the test and the control groups would have to be very large.

As such an experiment in man is not feasible, the judgment of causality must be made on other grounds. The epidemiologic method, when coupled with clinical or laboratory observations, can provide the basis from which judgments of causality may be derived.

INDIRECT MEASURE OF THE ASSOCIATION

The crudest indicators of an association between lung cancer and smoking are certain indirect measures: (a) a correlative increase in lung cancer mortality rates and in per capita tobacco consumption in a number of countries (76, 138, 211, 239, 255), and (b) disparities between male and female lung cancer mortality rates correlated with corresponding differences in smoking habits of men and women, both by amounts smoked and duration of smoking (65, 151, 344).

Figure 9 shows a correlation of crude male death rates from lung cancer in 11 countries in 1950 with the per capita consumption of cigarettes in these countries in 1930 as presented by Doll (76). Assuming a 20-year induction period for the appearance of lung cancer, Doll found a significant correlation (0.73 ± 0.30) between the death rates and cigarette consumption. Since virtually all the tobacco consumption in 1930 was among men in the countries

CRUDE MALE DEATH RATE FOR LUNG CANCER IN 1950 AND PER CAPITA CONSUMPTION OF CIGARETTES IN 1930 IN VARIOUS COUNTRIES.

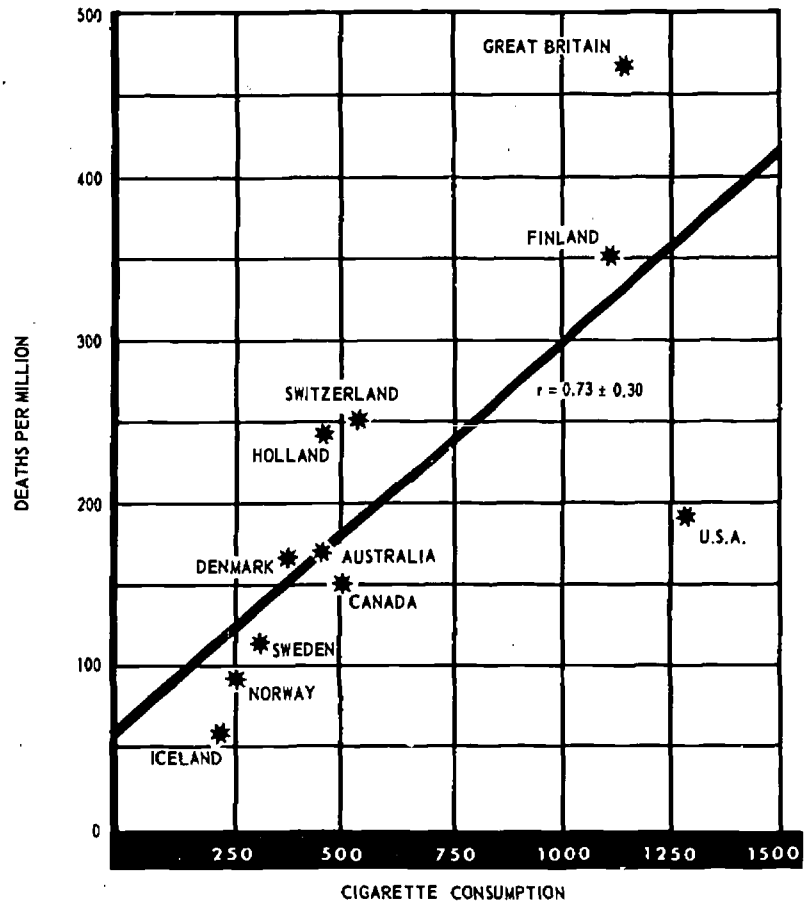


FIGURE 9.

Source: Doll, R (76)

represented (Great Britain, Finland, Switzerland, Holland, the United States, Australia, Denmark, Canada, Sweden, Norway, and Iceland), it seemed reasonable to compare the annual per capita consumption of each country with the crude, male lung cancer death rates.

It will be noted in Figure 9 that the data from the United States show a relatively low death rate in relation to cigarette consumption. Doll suggested two explanations: the influence of a higher proportion of young

people in the U.S. population and the method of smoking, with the U.S. smokers consuming less of each cigarette than the British smokers. Since Doll's explanations of the discrepancy, additional information has become available. Studies on length of cigarette butts discarded have shown American discards to be significantly longer than British discards; 30.9 mm (156) and 18.7 mm (85) respectively. Also, there is a significantly greater percentage of smokers in Great Britain than in the United States in the age groups in which lung cancer occurs at high rates (52.6 percent in 60+ year age group and 29.2 percent in 65+ year age group respectively).

Strictly comparable data do not exist on inhalation practices for the two countries. Such information would aid in explaining this discrepancy as well as a similar disparity between Holland and Great Britain. In Holland (156) the length of the cigarette butts was almost the same as in Great Britain (19.7 mm), but the crude male lung cancer death rate in Holland was significantly lower than in Great Britain. This correlates well, as shown in Figure 9, with the annual per capita consumption of cigarettes in Holland which has been much lower than in Great Britain.

It should be mentioned that differences in intensity of air pollution and industrial exposures in these countries have not been taken into account. However, for reasons given below, these latter factors do not account for the magnitude of the difference in incidence of lung cancer nearly as well as the amount of each cigarette smoked and the degree of inhalation. Finally, the varying composition of the tobacco in the several countries was not considered in these studies.

An elaboration of the disparities between male and female lung cancer mortality rates and their correlation with differences in smoking patterns is also in order, for the sex disparity has also been posed as contradictory to the smoking-lung cancer hypothesis. Although the opponents of the hypothesis, pointing to the sex disparity (116, 229), have minimized the differences in smoking habits, the fact remains that the magnitudes of the differences are quite large. In a representative cross-sectional survey of smoking habits coupled with the Current Population Survey of the Bureau of the Census in 1955, Haenszel, et al. (151) found the following disparities between male and female smoking patterns:

1. Whereas only 22.9 percent of males had *never* smoked, 67.5 percent of females had not.
2. Males showed relatively little variation among the component age groups in percentage not smoking, whereas females after age 25–34 showed a consistently increasing percentage of non-smokers in successively higher age groups (Figure 10).
3. Sixty-five percent of males smoked cigarettes as compared with 32 percent of females.
4. Cohort analyses revealed the adoption of cigarette smoking late in life for both males and females among cohorts born before 1890; but male cohorts born after 1900 successively began to smoke earlier in life. Large-scale adoption of cigarette smoking by women did not occur until the decades of the 1920's and 1930's.

PERCENTAGE OF PERSONS WHO HAVE NEVER SMOKED, BY SEX AND AGE, UNITED STATES, 1955

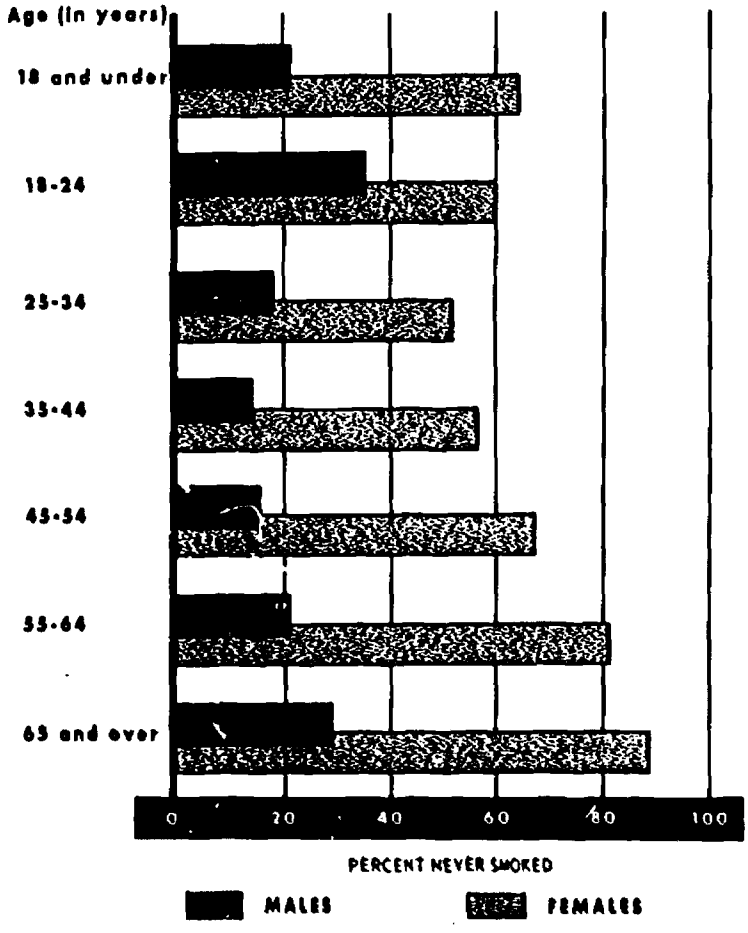


FIGURE 10.

Source: Haenszel, W. M. et al. (151)

5. The median age at which males started smoking has remained fairly stable for the several age cohorts: from 19.3 years for ages 65 and over to 17.9 years for age 25–34; the median age that females started smoking has dropped dramatically from 39.9 years for the age group 65 and over to 20.0 years for age 25–34.
6. Males in all age groups smoked considerably more cigarettes per day than did females. In ages 55 and over, 6.9 percent of the

males smoked more than a pack a day, compared with only 0.6 percent of the females. Although urban-rural and geographic regional differences were noted, significant disparities between male and female smoking were maintained throughout. Thus it can readily be deduced that these findings are consistent not only with the sex disparity in lung cancer mortality but also with the slower but nevertheless continuing rise in female lung cancer mortality.

British studies (344) also revealed that females, especially before World War II, consumed much less tobacco than did males. A correction for the marked disparity in smoking habits of males and females reduced the observed 5-fold excess of male lung cancer deaths to a 1.4-fold excess as of 1953 (149). Supporting this finding are the data from two retrospective studies (147, 152) in which the age-adjusted lung cancer death rates in 1958–59 among male and female non-smokers were 12.5 and 9.4 respectively for a ratio of 1.33 (145). This residual ratio implies that there may be other factors operating to produce a portion of the sex differential in mortality.

DIRECT MEASURE OF THE ASSOCIATION

For a direct measure of the association between lung cancer and smoking it is, of course, essential that both variables or attributes be measured in the same populations. The 29 retrospective studies, described earlier, consider smoking (usually kind, amount, and duration) and non-smoking among cases of lung cancer and individuals without lung cancer. The seven prospective studies consider the occurrence or lack of occurrence of lung cancer among smokers and non-smokers.

ESTABLISHMENT OF ASSOCIATION.—A number of investigators, though accepting the existence of an association, have questioned its significance in terms of a causal hypothesis (58, 102, 114, 115, 116, 117, 141, 178, 218, 219, 287, 288, 298, 299). Some of these doubts have been on the basis of a possible genetic underlay which might determine both smoking and lung cancer (114, 115, 116, 117). Some have followed contradictory observations in the dissenter's own work (58, 102, 141), incorrectly assessed evidence of lung cancer mortality trends, or the belief that the causal hypothesis requires cigarette smoking to be the sole cause of lung cancer (178, 287, 288). Others believe that the lung cancer rise is spurious and can be attributed either to improvements in diagnosis and reporting (218, 219, 287, 288, 298, 299) or to the aging of the population. In the latter explanation they ignore the fact that aging of the population does not affect age-specific mortality rates which, for lung cancer, are also rising with the passage of time. Still others express doubt on the basis of the lack of a concomitant rise in cancers of the oral cavity (178, 298) or of the skin of the fingers (178). Finally, some doubts have been based on supposed incongruencies between the cigarette-smoking hypothesis and urban-rural as well as sex differences in lung cancer mortality (116, 178, 229). There are a few investigators who maintain that the association may be spurious or that it has not been proved (22, 23, 24, 228, 229, 230).

A number of these objections have been assessed in earlier discussions in this section; others will be evaluated below. These latter criticisms have revolved about defects inherent in the retrospective or the prospective

methods of approach, biases of selection in either method, biases of non-response, the validity of the results in the early phases of a prospective study, and the misclassification of both variables: smoking habits and lung cancer.

It should be noted that the Current Population Survey of 1955 yielded results highly consistent with data on tobacco production and taxation (151); that classification errors in terms of amount of smoking were relatively minor in a reliability study by Finkner (113); and that, in at least three prospective studies, in which subjects were requestioned on smoking habits at intervals of at least two years, the replies were closely reproducible (87, 88, 157, 159, 162, 163), particularly if no illness had intervened (159).

With regard to the retrospective studies, it has also been suggested that knowledge of the illness might have introduced bias in relation to histories of smoking habits (158, 229). In at least one retrospective study, both patient and interviewer were unaware of the diagnosis of lung cancer, the smoking histories having been obtained before the diagnosis was made (207). Furthermore, patients initially believed to have lung cancer who, after interview, were found not to have the disease, reported smoking histories similar to the control groups and not the lung cancer groups (84). Finally, this bias cannot have influenced the findings of several studies in which a significantly greater proportion of cigarette smokers and heavy cigarette smokers were associated with epidermoid cancers than with adenocarcinoma (86, 150, 163, 313, 375). The reliability of response to smoking history would thus appear to be markedly above the critical level for the firm establishment of an association by the retrospective method. In prospective studies, this factor is less of a problem.

In retrospective studies the investigator can confine himself to cases with accurate diagnoses. In the prospective approach, accuracy of diagnosis may not always be attainable, but all cases must be included. In assessing the results of the prospective studies it must be kept in mind that all deaths from any cause were involved in the calculations, with the cigarette smoker rates higher than those for non-smokers and with a gradient by amount of smoking demonstrated in all of the studies. Evidence that the specific estimates of risk for lung cancer among smokers actually might have been underestimated has been presented by Hammond and Horn (162, 163), who found higher relative risk ratios among smokers for confirmed cases than for those with less well-established diagnoses. Most of the prospective studies yield relative risks of lung cancer by various smoking categories which approximate those found in the Doll and Hill physician study (83) where, obviously, diagnostic evidence would be more readily available than in the general population. It would thus appear that in the data from retrospective and prospective studies, diagnostic accuracy was not a critical factor in the establishment of an association between smoking and lung cancer.

The question of *selection bias* is, of course, a more complicated problem. Several criticisms have been leveled at both the retrospective and prospective methods. Although in retrospective studies the selection of a control group may pose a more serious problem, even the selection of the case material may interject difficulties. It has been claimed by Berkson (24) that the selection of hospitalized cases may lead to bias if smokers with lung cancer

were more often hospitalized than non-smokers with the disease. However, nearly all lung cancer cases are hospitalized, a point which, he concedes, would thus minimize this bias. Furthermore, several retrospective studies have surveyed all the cases in the area regardless of hospitalization (238, 335), or all deaths regardless of cause or hospitalization (379).

Another criticism of patient selection in retrospective studies deals with the danger that, in studies highly cross-sectional in time, if smokers live longer than non-smokers, there would obviously be more smokers in the disease group, and thus a spurious association of disease with smoking would result (254). There is no evidence for this basic assumption. Furthermore, it is inapplicable because almost all the retrospective studies were actually based on newly diagnosed cases collected serially over an interval of time long enough to remove this bias.

Control groups pose a problem in retrospective studies. In 27 of the 29 retrospective studies (exceptions are references 147 and 152) the controls were subjects without lung cancer, such as patients with other cancers, with diseases other than cancer, or so-called normals selected from the population. Analysis of the prospective studies proved that the biases interjected by the selection of sick controls in the retrospective studies actually operated to produce an underestimation of the association, for it has been shown that a number of other diseases are also associated with smoking. Furthermore, several studies have, in addition to controls with other diseases, selected a second set of random controls from the general population (82, 150, 222), only to find that the association utilizing sick controls, significant though it proved to be, was intermediate to the association utilizing random population controls.

The problem of selection bias in prospective studies is much more subtle, since there may be self-selection on the basis of illness existing at the time the study begins. This is essentially a problem of non-response which has been handled in detail in Chapter 8. The character of this non-response presents at least two nuances: a combination of self-selection and operator selection, as in the volunteer studies of Hammond and Horn (162) and Hammond (157) and the response to questionnaires in a total population study such as Dorn's (88).

Suffice it to say at this point that, regardless of whether there is over-representation of sick smokers or well non-smokers or both in a prospective study, with the passage of time more deaths of sick persons would occur (without regard to the independent variable of smoking). Thus the death rates of smokers would tend to approach the death rate of non-smokers, removing the original selection bias and providing greater confidence in the residual association of the death rate with smoking if it persisted. In two of the studies (157, 162, 163) exclusion of ill persons on entry did take place. Further, in the studies that provide this comparison, the high lung cancer mortality ratio of cigarette smokers was maintained with the passage of time. In the Dorn study the mortality ratio was 9.9 after three years experience and 12.0 after six years experience; the Hammond study gave 9.0 after 10.5 months (157) and 9.6 after 22 months, while Doll and Hill (84) showed that the gradient of increase in lung cancer death rate with increasing amount smoked appeared consistently in each of the first four years of their study.

This also weakens the criticism by Mainland and Herrera (230) of the use of non-professional volunteer workers for subject selection.

Thus it would appear that an association between cigarette smoking and lung cancer does indeed exist.

CAUSAL SIGNIFICANCE OF THE ASSOCIATION.—As already stated, statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability. To judge or evaluate the causal significance of the association between cigarette smoking and lung cancer a number of criteria must be utilized, no one of which by itself is pathognomonic or a *sine qua non* for judgment. These criteria include:

(a) The consistency of the association
(b) The strength of the association
(c) The specificity of the association
(d) The temporal relationship of the association
(e) The coherence of the association.

THE CONSISTENCY OF THE ASSOCIATION.—This criterion implies that diverse methods of approach in the study of an association will provide similar conclusions. It is noteworthy that all 29 retrospective studies found an association between cigarette smoking and lung cancer. The very nature of the criticisms leveled against these retrospective studies indicates a diversity of characteristics of approach and, for that matter, marked differences in shortcomings which have been discussed in detail above. It is indeed remarkable that no reasonably well designed restrospective study has found results to the contrary. Seven prospective studies have also revealed highly significant associations. Where relative risks could be calculated on the basis of some reasonable assumptions in some of the retrospective studies, a consistency not only among them (38, 82, 147, 152, 222, 283, 301, 313, 381) but also with the prospective studies could be demonstrated. Such a situation would prevail if the association were either causal, or spurious on the basis of an unknown source of bias. It is difficult to conceive of a universally acting bias in all the diverse approaches unless it be a constitutional genetic characteristic or one acquired early in life, which will be discussed later in the section, Constitutional Hypothesis.

Two studies of tobacco workers (58, 141) have been cited as inconsistent with the 29 retrospective and particularly the 7 prospective studies cited in detail in the early portions of this section. Both these studies can be dismissed because of major defects in methodology and concept. The heavier smoking among the tobacco workers in these studies was considered, but no comparison of observed-to-expected rates was made on the basis of smoking classes within this population. Furthermore their conclusions are based on expectancies in the general population without regard to the fact that persons with acute, chronic, or disabling illness are initially excluded from employment and that those developing permanent illness are lost to employee rolls.

THE STRENGTH OF THE ASSOCIATION.—The most direct measure of the strength of the association between smoking and lung cancer is the ratio of lung cancer rates for smokers to the rates for non-smokers, provided these two rates have been adjusted for the age characteristics of each group. Another way of expressing this is the ratio of the number of observed cases

in the smoker group to the expected number calculated by applying the non-smoker rate to the population of smokers. This provides us with a measure of relative risk which can yield a judgment on the *size of the effect* of a factor on a disease and which, even in the presence of another agent without causal effect, but correlated with the causal agent, will not be obscured by the presence of the non-causal agent. Cornfield et al. (62) have not only provided us with a detailed analysis of the applications of both absolute and relative measures of risk, but have also demonstrated the usefulness of the relative risk measure in judging causal and non-causal effects with mathematical proof of their statements.

An absolute measure of difference in prevalence of a disease between populations with or without the agent (e.g., cigarette smoke), where the agent may be causal in its effect on several diseases, can provide us with the means of appraising the public health significance of the disease, i.e. the size of the problem, in relation to other diseases. It is less effective for appraising the non-causal nature of agents having apparent effects, the importance of one agent with respect to other agents, or the effects of refinement of disease classification. This, Cornfield and his co-authors (62) have demonstrated.

In essence, then, a relative risk ratio measuring the strength of an association provides for an evaluation of whether this factor is important in the production of a disease. In the data of the nine retrospective studies for which relative risks of lung cancer among smokers and non-smokers were calculated, the ratios were not only high in all of the studies but showed a remarkable similarity in magnitude. More important, in the seven prospective studies which inherently can reveal direct estimates of risks among smokers and non-smokers, the relative risk ratios for lung cancer were uniformly high and, again, remarkably close in magnitude. Furthermore, the retrospective and prospective studies yielded quite similar ratios.

Important to the strength as well as to the coherence of the association is the dose-effect phenomenon. In every prospective study that provided this information, the dose-effect was apparent, with the relative risk ratio increasing as the amount of tobacco (84) or of cigarettes (25, 88, 96, 97, 163) smoked per day increased (Table 5). Even the retrospective studies for which relative risks were calculated by amount smoked (38, 147, 152, 222) showed similar increases in risks with amount smoked (Table 4).

It may be estimated from the data in the prospective studies that, in comparison with non-smokers, average smokers of cigarettes have a 9- to 10-fold risk of developing lung cancer, and heavy smokers, at least a 20-fold risk. Thus it would appear that the strength of the association between cigarette smoking and lung cancer must be judged to be high.

THE SPECIFICITY OF THE ASSOCIATION.—This concept cannot be entirely dissociated from the concept inherent in the strength of the association. It implies the precision with which one component of an associated pair can be utilized to predict the occurrence of the other, i.e., how frequently the presence of one variable (e.g., lung cancer) will predict, in the same individual, the presence of another (e.g., cigarette smoking).

In a discussion of the specificity of the relationship between any factor possibly causal in character and a disease it may produce, it must be rec-

ognized that rarely, if ever, in our biologic universe, does the presence of an agent invariably predict the occurrence of a disease. Second, but not less important, is our growing recognition that a given disease may have multiple causes. The ideal state in which smoking or smoking of cigarettes and every case of lung cancer was correlated one-to-one would pose much less difficulty in a judgment of causality, but the existence of lung cancer in non-smokers does indeed complicate matters somewhat. It is evident that the greater the number of causal agents producing a given disease the less strong and the less specific will be the association between any one of them and the total load of the disease. But this could not be posed as a contradiction to a causal hypothesis for any one of them even though the predictive value of any one of them might be small. For example, the pathologist who examines a lung at autopsy and finds tubercle formation and caseation necrosis would almost invariably be able to predict the coexistence of tubercle bacilli. Experience has shown that the lesions are highly specific for *Mycobacterium tuberculosis*. On the other hand, a clinician may encounter a combination of signs and symptoms including stiff neck, stiff back, fever, nausea, vomiting, and lymphocytes in the spinal fluid. Experience has revealed that any one of a number of organisms may be associated with this syndrome: polio virus, ECHO viruses, Coxsackie viruses and *Leptospirae*, to name but a few. The predictability of the coexistence of polio virus per se is rather low. In other words, the syndrome as noted is not very specific for polio virus. This may well be the condition which prevails in coronary heart disease where the mortality ratio is between 1.6 and 1.8 or a 60 to 80 percent excess among smokers of cigarettes. If this ratio is applicable to the entire population from which the sample data are derived, another way of expressing this relationship is that, of the total load of coronary heart disease mortality among males only 61 to 64 percent is associated with cigarette smoking. The large residual among non-cigarette smokers implies either other causes in addition to smoking or, as a somewhat greater possibility, factors actually causally related to coronary heart disease and frequently, but not invariably, associated with smoking.

However, in lung cancer, we are dealing with relative risk ratios averaging 9.0 to 10.0 for cigarette smokers compared to non-smokers. This is an excess of 900 to 1,000 percent among smokers of cigarettes. Similarly, this means that of the total load of lung cancer in males about 90 percent is associated with cigarette smoking. In order to account for risk ratios of this magnitude as due to an association of smoking history with still another causative factor X (hormonal, constitutional, or other), a necessary condition would be that factor X be present at least nine times more frequently among smokers than non-smokers. No such factors with such high relative prevalence among smokers have yet been demonstrated.

Another aspect of specificity requires some insight. Several critics of the causal hypothesis have questioned the significance of the association on the grounds that the existence of an association with such a wide variety of diseases, as elicited in the prospective studies, detracts from specificity for any one of them (22, 7). In a sense, this viewpoint is an exaggeration, for not all the specific disease mortality ratios in excess of 1.0 are large

enough to warrant secure judgments of the strength of the association and of causal significance. A detailed discussion of this latter point has been presented in Chapter 8. The number of diseases in which the ratios remain significantly high, after consideration of the non-response bias, is not so great as to cast serious doubt on the causal hypothesis. Even if we were dealing with a single pure substance in the environment, the production of a number of disease entities does not contradict the hypothesis. It is well known that a single substance may have several modes of action on the several organ systems and that neither inhalation nor ingestion implies action restricted to the respiratory or digestive tracts, respectively. In tobacco we encounter a complex of substances whose additive and synergistic characteristics before and after combustion remain inadequately explored. It would not be surprising to find that the diverse substances in tobacco smoke could produce more than a single disease.

Actually, the finding that an excess risk for smokers does *not* occur for every one of the causes of death reinforces the specificity of the excess risk for those causes where the excess is significant.

Thus, it is reasonable to conclude that the association between cigarette smoking and lung cancer has a high degree of specificity.

TEMPORAL RELATIONSHIP OF ASSOCIATED VARIABLES.—In chronic disease, insidious onset and ignorance of precise induction periods automatically present problems on which came first—the suspected agent or the disease. In any evaluation of the significance of an association, exposure to an agent presumed to be causal must precede, temporally, the onset of a disease which it is purported to produce. The early exposure to tobacco smoke and late manifestation of lung cancer among smokers, seem, at least superficially, to fulfill this condition. This does not, however, preclude the possibility that such patients who, many years after the initiation of smoking are diagnosed as having lung cancer, may have had the primitive cellular changes or anlage (as postulated by Cohnheim) before the advent of their smoking. However, no evidence has thus far been brought forth to indicate that the initiation of the carcinomatous process in a smoker who developed lung cancer antedated the onset of smoking.

COHERENCE OF THE ASSOCIATION.—A final criterion for the appraisal of causal significance of an association is its coherence with known facts in the natural history and biology of the disease. In the lung cancer-cigarette smoking relationship the following should be noted:

(1.) Rise in Lung Cancer Mortality.—The increases in per capita consumption of cigarettes (76, 138, 211, 239, 255) and the age-cohort patterns of smoking among males and females (151) are highly compatible with a real increase in lung cancer mortality.

(2.) Sex Differential in Mortality.—The current sex differences in tobacco use (151, 160), the pronounced differences in age-cohort patterns between males and females, particularly in the older age groups—over 55 (151) and over 50 (160)—and the more recent adoption of cigarette smoking by women (151, 344) are *all compatible with the high male-to-female* ratio of lung cancer mortality and also with the lower ratios of 30 years ago (130). Haenzel and Shimkin (149) developed a statistical model for determining whether the results of the retrospective and prospective studies

"were compatible with the information on distribution of lung cancer and thus valid for generalization to larger populations." Applying their model of scheduled relative risks to data on cigarette consumption by age and sex derived from the Current Population Survey of 1955, their predicted male/female ratio came quite close to the observed ratio in the general population.

(3.) Urban-Rural Differences in Lung Cancer Mortality.—A number of sources in this country (90, 136, 148, 175, 238, 252) and overseas (82, 199, 335) have firmly established the existence of an urban excess in lung cancer mortality. Because of the possible implication of an air pollution effect, this urban lung cancer mortality excess has been cited as either being incompatible with the smoking-lung cancer hypothesis (178, 229) or minimizing its significance (69, 70, 71, 101, 190). The data of the studies of a number of authors have clearly shown, however, that although adjustment for smoking history does not equalize the urban-rural lung cancer mortality ratio (149), control on the urban-rural residence factor nevertheless leaves a large mortality risk difference between smokers and non-smokers. Haenszel has demonstrated this fact in his two population sample studies on males and females (147, 152). Mills and Porter (238) demonstrated a much greater effect of smoking on lung cancer mortality than the urban-rural factor. Stocks (335) also demonstrated that though smoking is not the sole factor, as manifested by a rural-urban gradient among non-smokers, it represented a much more preponderant factor in accounting for the lung cancer mortality than did presumed air pollution or at least urbanization. He noted that his regression lines on amount smoked were parallel for the different areas in England and North Wales and that the urban-rural mortality ratios declined from 2.3 among non-smokers and 2.5 among light cigarette smokers to unity among heavy smokers. The first prospective study of Hammond and Horn (162) also showed higher lung cancer mortality rates irrespective of residence. In Dean's second study in South Africa (70), in which he corrected the critical defect in his first study of not studying the smoking habits of the test populations, he continued to emphasize urbanization or air pollution as the major factor in lung cancer. A perusal of his data, however, shows that by controlling on smoking, the lung cancer mortality rates are doubled by the factor of country of origin; whereas, with country of origin controlled, the lung cancer risk increases from 3 to 20 times as the amount of cigarette smoking increases. After smoking patterns are controlled, the residuals in the urban over rural excess imply other factors, although the smoking factor preponderates in the urban-rural differences in lung cancer mortality in all of these studies. Thus the urban excess of lung cancer mortality is not incompatible with the smoking-lung cancer hypothesis.

(4.) Socio-Economic Differentials in Lung Cancer Mortality.—Distinct socio-economic differentials have been demonstrated convincingly in the epidemiology of lung cancer. Cohart (57) found a 40-percent excess of lung cancer incidence among the lowest economic class (both sexes) in the New Haven population, and the morbidity survey by Dorn and Cutler (90) demonstrated a distinct gradient by income class among white males, with the highest rates among the lowest income groups. In Denmark, Clemmesen and Nielsen, utilizing data derived from the Danish Cancer Registry, also

found a much higher incidence of lung cancer among males in the lower rental groups (55). In relation to the contribution which smoking makes to this differential, there is evidence that cigarette smoking may be inversely related to socio-economic status. The components of socio-economic status are, at best, difficult to define, compartmentalize, and measure. Direct inquiries of family income are rare and, when made, are subject to considerable error. Studies based on rental values, as in the Danish studies, express more adequately socio-economic status.

Another high correlate of income is educational achievement, which has been considered by Hammond in his current prospective study (161) in relation to smoking habits. Among males, the highest proportion of cigarette smokers (past or present) and the highest proportion of those smoking 20 or more cigarettes per day (past or present) were found in the group classified as "some high school education (but not high school graduates)," whereas the lowest proportion was found among college graduates. The highest proportion of ex-cigarette smokers (as of 1961–62) was among college graduates. Although the relation of smoking and educational level in women is more complicated, the group which had been to college also had the highest proportion of ex-smokers. Finally, college graduates had the next to the lowest proportion of heavy cigarette smokers. None of the female gradients was a sharp as those for the men.

Occupation has also been utilized as a measure of socio-economic status, but this measure obviously has severe limitations. No definitive study has been reported in which lung cancer has been correlated with occupation and smoking class; the current Hammond (157) and Dorn (88) prospective studies may ultimately yield definitive findings in this regard. However, some indirect evidence of a partial correlation between the observed higher lung cancer death rates in lower socio-economic groups may be found in Table 26 of the Survey of Tobacco Smoking Patterns in the United States (151). Keeping in mind that type of occupation is not a critical index of income, it will nevertheless be noted that the professional and farmer and farm manager groups had higher proportions of non-smokers among them than did the laborers and craftsmen. This finding is in the proper direction for compatibility with the socio-economic differential in lung cancer mortality but the disparity does not appear to be sufficient to provide a satisfying correction. In fact, in this U.S. study, analyses by amount of cigarettes smoked tended to obscure the ordering by social class. In Great Britain, however, the inverse relationship of socio-economic class to heavy cigarette smoking remained apparent (174). In the U.S. study, classification by industry showed the highest proportions of non-smokers to be in the professional and agricultural groups and the lowest among industries. Thus, though the measures are admittedly crude, they are compatible with the socio-economic differential in lung cancer mortality.

(5.) The Dose-Response Relationship.—If cigarette smoking is an important factor in lung cancer, then the risk should be related to the amount smoked, amount inhaled, duration of smoking, age when started smoking, discontinuance of smoking, time since discontinuance, and amount smoked prior to discontinuance. Herein lies the greatest coherence with the known facts of the disease. In almost every study for which data were adequate

and which was directed to amount of smoking, duration of smoking and age when smoking was begun, the associations or calculated relative risks (direct or indirect) revealed gradients in the direction of supporting a true dose effect. Where discontinuance, time since discontinuance, and amount smoked prior to discontinuance were considered in either retrospective studies or, with more detail, in prospective studies, these all showed lower risks for ex-smokers, still lower risks as the length of time since discontinuance increased, and lower risks among ex-smokers if they had been light smokers. These findings have been described in detail in the section on Retrospective Studies.

Some contradictory information has been presented in regard to inhalation of tobacco smoke. This is the lack of association between inhalation and lung cancer as noted by Doll and Hill (82) alluded to earlier. These authors have begun collecting data (in their prospective study) on inhalation for the mortality experience since 1958. These data are not presently available (80). However, until the current ongoing prospective studies will have yielded information on this point in regard to lung cancer, four retrospective studies provide information on inhalation contrary to the Doll and Hill early negative findings (38, 211, 222, 313). In two of these (222, 313) inhalation and amount of smoking were considered and led to the provocative finding that with increase in daily amounts of cigarettes smoked the differences in risks between inhalers and noninhalers diminished. There is no immediate explanation for this apparent discrepancy.

Hammond has studied the smoking habits of the men and women in his current prospective study quite intensively (160). He has observed that the majority of men (92.9 percent) who smoke cigarettes inhale, and of these the majority inhale "moderately" to "deeply." Pipe or cigar smokers inhale rarely. Combination smokers (i.e., cigarettes in combination with pipes and/or cigars) inhale in proportions intermediate to these. These findings become compatible with the hypothesis that the degree of inhalation accounts for a gradient of lung cancer risks, high to low, for smokers of cigarettes only, combination smokers, and pipe or cigar smokers (Table 5). An explanation of the diminishing differences in risks between "inhalers" and "noninhalers" with increase in amount smoked might be obtained if a more objective measure of inhalation were available.

(6.) Localization of Cancer in Relation to Type of Smoking.—Although historically a relationship between cancer and smoking was suspected by Holland (176) and Soemmerring (322) with reference to the lower lip, it was not until the systematic, controlled study of lung, lip, pharynx, esophagus, colon and rectum cancers in relation to types of smoking by Levin in 1950 that significantly distinctive associations between localization of the cancer and type of smoking were elicited (207). Levin noted that statistical significance was achieved for cigarette smoking and lung cancer and for pipe smoking and lip cancer and stated, "It is somewhat surprising that type of smoking is the associated factor, rather than the actual use of tobacco." Since then other studies have pointed up the relationship between type of smoking and localization of cancer. Sadowsky (301) in relative risk estimations of types of smoking and cancer site, also noted the highest significant values for cigarettes with lung, larynx and esophagus; for pipes with lip,