
The Health Consequences of SMOKING

A PUBLIC HEALTH SERVICE REVIEW : 1967



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Foreword

The Federal Cigarette Labeling and Advertising Act of 1965 (Public Law 89-92) requires that the Secretary of Health, Education, and Welfare submit regular reports to the Congress on the health consequences of smoking, together with any legislative recommendations he may wish to make.

This 1967 Surgeon General's Report was prepared to provide the Secretary and the public with a review of the research findings which have taken place in smoking and health in the approximately 3½ years which have elapsed since the Surgeon General's Advisory Committee issued its monumental 1964 report. Part I of this document was included as part of the Secretary's 1967 Report which he sent to Congress in July 1967. Part II, which provides detailed discussions of the relationship of smoking to specific diseases, is issued here for the first time.

The 1967 report represents a review of more than 2,000 research studies published since the 1964 report. These additional studies confirm and strengthen the conclusion of the Surgeon General's Advisory Committee that: "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action."

In a separate section of this report, acknowledgments have been made for the help of numerous scientists both within and outside the Public Health Service, who participated in the preparation of this report. These include the 10 distinguished scientists who made up the Surgeon General's 1964 Advisory Committee, all of whom were kind enough to review part I of the 1967 report before its publication. A special word of thanks is due Leonard M. Schuman, M.D., one of the 1964 committee members, who advised the staff in the final editing of the entire document.

William H. Stewart
SURGEON GENERAL.

Table of Contents

	Page
Part I. Current Information on the Health Consequences of Smoking.....	1
Introduction.....	3
Smoking and Overall Mortality.....	7
Some General Considerations.....	11
Smoking and Overall Morbidity.....	19
Smoking and Cardiovascular Diseases.....	25
Smoking and Chronic Bronchopulmonary Diseases (Non-neoplastic).....	29
Smoking and Cancer.....	33
Other Conditions and Areas of Research.....	39
Cited References.....	41
Part II. Technical Reports on the Relationship of Smoking to Specific Disease Categories.....	43
Chapter 1. Smoking and Cardiovascular Diseases.....	45
2. Smoking and Chronic Bronchopulmonary Diseases (Non-neoplastic).....	87
3. Smoking and Cancer.....	125
4. Other Conditions and Areas of Research.....	179

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PART 1

Current Information on the Health Consequences of Smoking

Introduction

In January 1964, an Advisory Committee appointed by the Surgeon General of the Public Health Service issued its report (15) on the relationship between smoking and health.* The conclusions of that Committee were summed up in the sentence: "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action."

In the 3½ years since the publication of that report, an unprecedented amount of pertinent research has been completed, continued, or initiated in this country and abroad under the sponsorship of governments, universities, industry groups, and other entities. This research has been reviewed and no evidence has been revealed which brings into question the conclusions of the 1964 report. On the contrary, the research studies published since 1964 have strengthened those conclusions and have extended in some important respects our knowledge of the health consequences of smoking.

The present state of knowledge of these health consequences can, in the judgment of the Public Health Service, be summarized as follows:

1. Cigarette smokers have substantially higher rates of death and disability than their nonsmoking counterparts in the population. This means that cigarette smokers tend to die at earlier ages and experience more days of disability than comparable nonsmokers.
2. A substantial portion of earlier deaths and excess disability would not have occurred if those affected had never smoked.
3. If it were not for cigarette smoking, practically none of the earlier deaths from lung cancer would have occurred; nor a substantial portion of the earlier deaths from chronic bronchopulmonary diseases (commonly diagnosed as chronic bronchitis or pulmonary emphysema or both); nor a portion of the earlier deaths of cardiovascular origin. Excess disability from chronic pulmonary and cardiovascular diseases would also be less.

*"Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service." It is frequently referred to in this manuscript as "the Surgeon General's 1964 Report."

4. Cessation or appreciable reduction of cigarette smoking could delay or avert a substantial portion of deaths which occur from lung cancer, a substantial portion of the earlier deaths and excess disability from chronic bronchopulmonary diseases, and a portion of the earlier deaths and excess disability of cardiovascular origin.

NATURE OF RECENT RESEARCH FINDINGS

Since the Surgeon General's Report was published in January 1964, there has been a proliferation of additional studies and reports on smoking research. In the 12 years preceding that report, some 3,000 articles were published reporting research; since 1964, there have been more than 2,000 additional studies.

These studies have helped to clarify the role that age plays in the relationship of smoking to health; the similarities and differences in the ways in which men and women are affected by smoking; and the influences and effects of stopping smoking, particularly in the case of lung cancer where there is significant data to show that sharp reductions in lung cancer deaths follow closely reductions in cigarette smoking. The studies also suggest the importance of a variety of measures of exposure; add substantial new information on the magnitude of the morbidity problem associated with smoking; and provide more adequate data upon which to base estimates of the magnitude of the mortality problem.

Historically, concern about the effects of smoking began with observations of the extremely high frequency with which lung cancer patients were identified as cigarette smokers. These observations took on a fuller meaning with the first publication of the prospective studies in 1954 when higher overall death rates among cigarette smokers were identified. The rates were found to exceed the difference that could be accounted for by lung cancer alone. Until that time, the possibility remained that although more cigarette smokers appeared to suffer from lung cancer, if there were no significant excess overall mortality, some other cause or causes of mortality would have had to be underrepresented among cigarette smokers.

The Surgeon General's 1964 Report concluded that cigarette smokers do have higher death rates than their nonsmoking counterparts. This has changed the emphasis of the present problem away from the question "does cigarette smoking cause disease?" to the more precise questions of:

1. How much mortality and excess disability are associated with smoking?

2. How much of this early mortality and excess disability would not have occurred if people had not taken up cigarette smoking?

3. How much of this early mortality and excess disability could be averted by the cessation or reduction of cigarette smoking?

4. What are the biomechanisms whereby these effects take place and what are the critical factors in these mechanisms?

To answer these questions one must not only study the details of the relationship of overall mortality with cigarette smoking, one must also turn to the specific causes of death and disability and to other kinds of evidence.

The research carried on since 1964 is of three principal varieties: Epidemiological studies, especially those which involve surveys of large portions of the population; a health survey which has revealed new information about the relation between smoking and illness; and a vast amount of experimental, clinical, pathological, and behavioral research which adds to the understanding of the precise ways in which smoking affects the body, plus other closely related or peripheral information.

In the area of morbidity or illness, the primary addition to our knowledge is from "Cigarette Smoking and Health Characteristics," a report (16) of the National Center for Health Statistics on the frequency of illness among smokers and nonsmokers in a large probability sample of the U.S. population. Regarding epidemiological data, new reports from four of the major population studies have been published since 1964:

1. The Dorn study of smoking and mortality among U.S. veterans (13).

2. Hammond's study on smoking in relation to the death rates of 1 million men and women in 25 States (11).

3. The Doll and Hill study on the mortality of British physicians in relation to smoking (8, 9, 10).

4. A Canadian Smoking and Health Study of Canadian pensioners, including veterans and dependents (1).

The principal features of the additional data provided by these four studies are: (1) The extension of the time period of followup, (2) the additional data available for specific age groups among men, and (3) the inclusion of substantial data on women. In all, the prospective study reports now available are based on more than 108,000 deaths, an increase of about 43,000 deaths over the 65,023 summarized in the 1964 report. About 19,000 of these additional deaths were among women.

THE NATURE OF THIS REPORT

This report which provides a summary of current information on the health consequences of smoking, is based on the review of the research reports which have become available since the study of the Surgeon General's Advisory Committee was released. Public Health Service staff members consulted the literature and requested additional information or interpretations of the published data from the research scientists when needed. During this review a complete bibliography, containing some 5,700 citations, was compiled; it is now in manuscript form and will be published shortly (19).

The advice and comments of experts within the Public Health Service, particularly the Bureau of Disease Prevention and Environmental Control and the National Institutes of Health, as well as of specialists outside the Public Health Service, were solicited especially on matters involving judgment and evaluation.

The general criteria used by the Surgeon General's Committee have been followed. First, epidemiological data were evaluated to determine whether an association exists. In judging the significance of the association, its consistency, strength, specificity, temporal relationship, and coherence were utilized. The convergence of evidence from animal experiments, clinical and autopsy studies, and population studies remains the essential basis for evaluation of the significance of the associations identified.

This report presents, under the following headings, the major findings of research studies published in the past 3 to 4 years:

1. Smoking and Overall Mortality.
2. Smoking and Overall Morbidity.
3. Smoking and Cardiovascular Diseases.
4. Smoking and Chronic Bronchopulmonary Diseases (Non-neoplastic).
5. Smoking and Cancer.
6. Other Conditions and Research Areas.

Each of these sections is introduced by pertinent conclusions from the Surgeon General's 1964 Report, which are followed by discussion and conclusions of the present study.

Smoking and Overall Mortality

CONCLUSIONS OF THE SURGEON GENERAL'S 1964 REPORT

CIGARETTE smoking is associated with a 70-percent increase in the age-specific death rates of males, and to a lesser extent with increased death rates of females. 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.

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 nonsmokers. For those who smoke from 10 to 19 cigarettes a day, it is about 70 percent higher than for nonsmokers; 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 nonsmokers, 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 nonsmokers, 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 noninhalers.

The ratio of death rates of smokers to that of nonsmokers is highest at the earlier ages (40-50) represented in these studies, and declines with increasing age.

Possible relationships of death rates to other forms of tobacco use were also investigated * * *. The death rates for men smoking less than 5 cigars a day are about the same as for nonsmokers. 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 nonsmokers, even for men who smoke 10 or more pipefuls a day and for men who have smoked pipes more than 30 years.

CURRENT INFORMATION, 1967

The primary addition to knowledge in the areas of smoking and overall mortality comes from the four major population studies. Additional periods of followup have provided a broader base from which it becomes possible to estimate the excess deaths related to cigarette smoking in the U.S. population and from which firmer conclusions may be drawn as to the role of various exposure factors in the associations found.

The contributions since 1964 of each of the four population studies to the relation of smoking and overall mortality, as summarized by the authors, are set forth below.

STUDY OF U.S. VETERANS

(An 8½ year followup of 293,658 persons holding U.S. Government life insurance policies. Commonly referred to as the Dorn Study after the late Dr. Harold F. Dorn. The most recent report is by Kahn (13).)

“* * * the increased mortality risk associated with cigarette smoking was found to be higher in the more recent calendar time period than in the initial years of the study.

“* * * mortality ratios of current cigarette smokers compared with those who have never smoked are 1.7 for death from all causes, 10.9 for lung cancer, 12.2 for emphysema without bronchitis, and 1.6 for coronary heart disease. Paralysis agitans was the only cause of death associated with significantly lower mortality for smokers than for nonsmokers.

“For all categories of current smokers, risk was related to amount smoked. The risk for cigarette smokers was much greater than that for pipe or cigar smokers. Current smokers of cigarettes, cigars, or pipes experienced a mortality risk significantly greater than that for nonsmokers if they smoked more than four pipes or four cigars daily or more than an occasional cigarette.

“There was a positive relationship between duration of cigarette smoking and mortality risk from all causes of death for at least some classifications of smokers.

“* * * probabilities of death for ex-smokers of cigarettes revealed a downward trend in risk as duration of time discontinued increased, when other variables—age began smoking, amount smoked, and current age—were controlled * * *. The data can be regarded as evidence against the constitutional hypothesis.”

Calculations are presented to note that observations made during the study suggest the possibility that data from respondents (those who answered the smoking questionnaire) may in fact underestimate

the risk associated with smoking. The Surgeon General's 1964 Report had considered the possibility that differences between respondents and nonrespondents to the questionnaire might have introduced a bias and had attempted to calculate a maximum estimate of that bias.

STUDY OF MEN AND WOMEN IN 25 STATES

(This report is based on 3,764,571 person-years of experience and 43,221 deaths occurring among 1,003,229 subjects—440,568 men and 562,671 women—between the ages of 35 and 84 from October 1, 1959, to February 15, 1960, when they enrolled in a prospective study and answered detailed questionnaires including questions on their smoking habits. Hammond. (11).)

“Death rates of both men and women were higher among subjects with a history of cigarette smoking than among those who never smoked regularly.

“Death rates of current cigarette smokers increased with number of cigarettes smoked per day and degree of inhalation.

“Death rates were higher among current cigarette smokers starting the habit at a young age than among those starting the habit later in life. Among both men and women, the difference between the death rates of cigarette smokers and nonsmokers increased with age.

“Among men, the death rates for ex-cigarette smokers were lower than for men currently smoking cigarettes when they enrolled in the study. Death rates of ex-cigarette smokers decreased with the length of time since they last smoked cigarettes.

“* * * Total death rates and death rates from most of the common diseases occurring in both sexes were higher in men than women, were higher in men who never smoked regularly than in women who never smoked regularly, and were far higher in men with a history of cigarette smoking than in women with a history of regular cigarette smoking.

“The difference between the death rates of subjects with a history of cigarette smoking and subjects who never smoked regularly was far greater among men than women. Female cigarette smokers (as a group) have been far less exposed to cigarette smoke than male cigarette smokers of the same ages, as judged by number of cigarettes smoked per day, degree of inhalation, and the number of years they have smoked. Many female cigarette smokers smoke only a few cigarettes a day, do not inhale, and have been smoking for only a few years; their death rates are about the same as the death rates of women who never smoked regularly.”

STUDY OF BRITISH PHYSICIANS

(The mortality of nearly 41,000 men and women in the medical profession in the United Kingdom has been followed for 12 years. During the

first 10 years 4,597 of the men and 366 of the women died. These deaths were analyzed in relation to smoking habits reported by doctors in reply to a questionnaire sent to them in 1951—both sexes—and again in 1967, men, and 1960, women. Doll and Hill (8, 9).)

“* * * An association with smoking is found, in differing degrees, in men for seven causes of death [which accounted for 39 percent of the death rate]—namely, cancer of the lung, cancers of the upper respiratory and digestive tracts, chronic bronchitis, pulmonary tuberculosis, coronary disease without hypertension, peptic ulcer, and cirrhosis of the liver and alcoholism. No association is found with the remaining 61 percent of the death rate, and this includes such major causes as other forms of cancer, cerebrovascular accidents, hypertension, myocardial degeneration, suicide, and accidents.

“In women, the few deaths at present available show an association only between smoking and cancer of the lung.

“* * * If the excess deaths in smokers under the age of 65 years from (a) cancer of the lung, (b) chronic bronchitis and emphysema, (c) coronary thrombosis without hypertension be taken as attributable to their cigarette smoking, then the total mortality from all causes at ages 45–64 years is increased thereby by approximately 50 percent.”

The report states: “One of the striking characteristics of British mortality in the last half-century has been the lack of improvement in the death rate of men in middle life. In cigarette smoking may lie one prominent cause.”

STUDY OF CANADIAN PENSIONERS

(The purpose of the study was to investigate the relationships between residence, occupation, smoking habits, and mortality from chronic diseases particularly lung cancer. It was initiated by a questionnaire which was sent to Canadian veteran pension recipients during the period September 1955 through June 1956.

Returns from 78,000 men, and 14,000 women, mostly widows, were analyzed. The men were mainly World War I and World War II veterans, but some Boer War and Korean War veterans, as well as some non-veteran pension recipients were included. The age of most of the men at the beginning of the study ranged from 30 to 90 years and the distribution was characterized by the ages of men eligible for service in the two World Wars.

For each respondent dying between July 1, 1956, and June 30, 1962, the cause of death was related to information on his questionnaire about age, history of smoking habits, residence and occupation. Among the respondents during the 6 years of followup there were 9,491 deaths of males, and 1,794 deaths of females which were analyzed (1.)

“Current cigarette smokers had a death rate for overall mortality 54 percent higher than that of nonsmokers * * * Ex-cigarette smok-

ers had a comparatively lower rate, which was still 36 percent above the rate for nonsmokers * * * Men smoking combinations of cigarettes plus cigars and/or pipe also had elevated death rates for overall mortality, but these were not elevated to the same extent as those of men smoking only cigarettes.

"The death rates for overall mortality of pipe smokers and cigar smokers were not appreciably different from those of nonsmokers.

"For cigarette smokers as compared to nonsmokers, overall mortality ratios were elevated after 5 years of smoking at any time in their life and remained elevated as long as they continued to smoke cigarettes.

"Male current cigarette smokers who inhaled had a death rate for overall mortality 52 percent higher than that of those who did not inhale.

"An urban/rural comparison was made between males of equivalent cigarette smoking habits and nonsmokers. It was found that the death rate for overall mortality of urban dwellers (persons with a history of 5 years or more of city residence) was 12 percent higher than that for rural dwellers of comparable smoking habits.

"Respondents were classified into occupational groups based on their history of occupation. No evidence was found in this study of clear-cut associations between cause of death and occupation. Further, occupation did not appear to modify the established association of cigarette smokers with death rates in excess of those of nonsmokers."

SOME GENERAL CONSIDERATIONS

The problem of how best to measure the relationship between smoking and mortality has been discussed in the Surgeon General's 1964 Report as well as in some of the prospective study reports. As the amount of data available increases, the person-years of observations in the many population subgroups that are worth examining increases so that stable rates may be computed and compared. A brief discussion of three measures of comparison available and their utility seems desirable as confusion frequently arises over these measures.

1. **Mortality Ratios:** Obtained by dividing the death rate for a classification of smokers by the death rate of a comparable group of nonsmokers.
2. **Differences in Mortality Rates:** Obtained by subtracting from the death rate for smokers, the death rate of a comparable group of nonsmokers.
3. **Excess Deaths:** Obtained by subtracting from the number of deaths occurring in a group of smokers, the number of deaths

which would have occurred if that group of smokers had experienced the same mortality rates as a comparable group of nonsmokers. In the example which follows this has been reported as a percentage of all deaths in the appropriate age group.

Table 1 presents in summary form all three measures for five age groups of men from both the U.S. veterans study and Hammond's study and for the same age groups of women from the latter study.

The statistics were derived from the cited publications to provide reasonable comparability and may vary slightly from the figures combined in other ways. Also it should be noted that the age groups are not defined identically and the experience reported covers somewhat different time periods. The smoking group analyzed is "current cigarette smokers," i.e., those who were smoking at the time of enrollment into the study, and the comparison group is "never smoked regularly," i.e., those who had never been regular smokers of any form of tobacco.

The number of deaths in each age-sex group is given to indicate the relative stability of the figures in that column. The data in the veterans study are largely concentrated in age groups 55-64 and 65-74. In Hammond's study, age group 35-44 is less stable than the succeeding groups both for men and for women.

1. *Mortality Ratios.*—For men, these are at their highest in age group 45-54, diminishing in each subsequent decade. In both studies mortality ratios appear to be somewhat lower in the preceding decade 35-44. However, with the smaller numbers of cases available in that age group, it may be that selective factors contribute to the finding. For women the mortality ratios are much smaller than for men, although the same pattern is suggested. In general, a mortality ratio has been considered to reflect the degree to which a classification variable identifies or may account for variations in death rates. As such, it is a measure of relative risk which indicates the importance of that variable relative to uncontrolled variables—an indicator of *potential biological significance*.

2. *Differences in Mortality Rates.*—These increase consistently with increasing age in all three study groups, except for the oldest age group in women where there is practically no difference in the rates for smokers and nonsmokers. Differences between smokers' rates and nonsmokers' rates are much smaller for women than for men, as are the death rates themselves for men and women classified similarly with respect to smoking. This measure reflects the added probability of death in a 1-year period for the smoker over that for the nonsmoker. As such it is a measure of *personal health significance*, a means for the individual to estimate the added risk to which he is exposed.

TABLE 1.—Comparison of 3 measures of relationship between cigarette smoking and overall death rates by age and sex as derived from 2 major prospective studies (11, 13)¹

	Age				
	35-44	45-54	55-64	65-74	75-84
U.S. VETERANS: MEN					
Total deaths.....	383	366	13,840	17,550	1,932
Death rates per 100,000:					
Never smoked regularly.....	127	264	1,056	2,411	6,214
Current cigarette smokers.....	232	728	1,819	4,032	8,471
Mortality ratio ²	1.83	2.76	1.72	1.67	1.36
Difference in death rates per 100,000 ³	105	464	763	1,621	2,257
Excess deaths as percentage of total ⁴	33	43	21	17	8
HAMMOND MEN					
Total deaths.....	631	5,297	8,427	8,125	3,968
Death rates per 100,000:					
Never smoked regularly.....	210	406	1,202	3,168	7,863
Current cigarette smokers.....	397	925	2,202	4,788	9,674
Mortality ratio ²	1.89	2.28	1.83	1.51	1.23
Difference in death rates per 100,000 ³	187	519	1,000	1,620	1,811
Excess deaths as percentage of total ⁴	33	38	25	13	4
HAMMOND WOMEN					
Total deaths.....	727	2,826	3,915	5,115	4,188
Death rates per 100,000:					
Never smoked regularly.....	165	304	698	1,913	5,914
Current cigarette smokers.....	186	384	838	2,229	5,846
Mortality ratio ²	1.13	1.26	1.20	1.17	.99
Difference in death rates per 100,000 ³	21	80	140	316	68
Excess deaths as percentage of total ⁴	5	9	4	2	-----

¹ These figures are derived from the references. 5 year age groups were combined directly from the reported statistics without adjustment to any standard population.

² Mortality ratios—Death rate for current cigarette smokers divided by death rate for those who never smoked regularly.

³ Difference in death rates—Death rate for current cigarette smokers minus death rate for those who never smoked regularly.

⁴ Excess deaths among current cigarette smokers (i.e., additional deaths that occurred among current cigarette smokers per year above those which would have occurred if smokers had the same death rates as those who never smoked regularly). This is expressed as a percentage of all deaths occurring in that age-sex group.

3. *Excess Deaths as a Percentage of Total Deaths*—As with mortality ratios, this statistic appears to be highest in the age group 45–54 where it reaches 43 percent in one group of men and 38 percent in the other. Hammond's data by 5-year age groups show the highest rate at ages 45–49, where it is 44 percent. Reviewing both study groups it appears that for men between the ages of 35 and 60 approximately one-third of all deaths that occur are excess deaths in the sense that they would not have occurred as early as they did if cigarette smokers had the same death rates as the nonsmoking group. For women, the percentage is much lower, reaching a peak of 9 percent of all deaths in age group 45–54. It should be noted that this measure not only depends on the differences in death rates between the smokers and the nonsmokers, but also on the proportion of smokers in the group. Thus, even with a large difference in rates between smokers and nonsmokers, a population with very few smokers would have very few excess deaths. This measure is therefore an indicator of the *public health significance* of the differences found since it measures the number of people affected and therefore the magnitude of the problem for society as a whole.

Once the magnitude of the excess is identified the problem becomes one of determining (1) how much of the excess would not have occurred if it had not been for cigarette smoking and (2) how much would have occurred anyhow. It should be noted that much of the excess has already been identified as belonging in the first category. Of the remainder, little of the excess has been clearly identified as belonging in the second category—that is, not caused by smoking. With most of that remainder there is uncertainty as to the category in which it belongs.

MEASURES OF EXPOSURE

Studies involving smoking, whether epidemiological or behavioral, have been concerned with measures of exposure to tobacco smoke. For the most part, these studies have been restricted principally to the index of number of cigarettes smoked over a specified period of time, usually an "average day." The heavy reliance on numbers of cigarettes alone as a measure has produced important findings but it has possibly obscured others. The new reports on the prospective studies have provided a substantial amount of data to support the concept that many elements should enter into an overall measure of exposure. Such factors as age at beginning smoking, duration of smoking, and inhalation have all shown some independent contributions to the overall effect, along with numbers of cigarettes. A recent report (12) has attempted to develop a more adequate measure of exposure in which various individual components of dosage would be combined to form composite scores.

A dosage score was developed as a function of the average number of cigarettes smoked per day, the "tar" (smoke solids minus moisture) rating of the brand of cigarette smoked, and the portion of the cigarette actually smoked. In addition, questions on both depth and frequency of inhalation were developed. Normative data have been obtained from a national survey sample of smokers. In general, although the various measures reflecting exposure are interrelated, there are many individuals with high exposure on one measure but low exposure on another. Furthermore, there are systematic differences in some of these measures of dosage between men and women, between heavy and light smokers (by the usual criterion of numbers of cigarettes), etc. The existence of a dose-response relationship between exposure to cigarette smoke and the risks most clearly associated with cigarette smoking is now generally accepted.

Wynder and Hoffmann (20) have shown in laboratory experiments with animals that the tumorigenicity of cigarette smoke can be reduced by alteration in the cigarette which reduces the "tar" and nicotine content. They use the term "indicator" for "tar" and nicotine content (the two measures tend to be used jointly since when one is high the other tends to be high unless the nicotine has been removed in processing), or other measures which reflect this type of relationship, lacking the identification of specific agents which are responsible for the effect. Bock, Moore, and Clark (21) have independently shown a similar variation in carcinogenic activity of tobacco "tar" obtained from different types of cigarettes.

The preponderance of scientific evidence strongly suggests that the "tar" and nicotine content of cigarette smoke is a meaningful factor in the measurement of dosage.

CESSATION OF SMOKING

The cessation of smoking is, of course, an extreme example of the reduction of dosage. Data from the prospective studies show a reduction in both overall mortality and mortality from specific diseases among those who have stopped smoking when compared with those persons who continue to smoke. This finding has been somewhat obscured by the fact that ill health is a frequent cause of giving up smoking so that death rates and disability rates for ex-smokers as a group tend to be high for an initial period of time following cessation.

In this connection, the Study of British Physicians shows that among the total group of physicians in the study (smokers, ex-smokers, and those who never smoked, combined) there was a reduction in the standardized lung cancer death rate from 0.69 per 1,000 in the first 5 years of the study (1951-56) to 0.64 per 1,000 in the second 5 years of the study (1956-61). This reduction occurred during

the time when there was also a substantial drop in cigarette smoking among physicians in general, and during the time that lung cancer rates were rising in the male population of Great Britain. This situation is not unlike that of a controlled cessation experiment in which the effect of giving up smoking is judged by the mortality results in an entire population in which the giving up of smoking is common as against another population in which it is not common. A more recent report by Doll (7) suggests that this trend is becoming more marked as the rate of smoking among British physicians decreases and the length of the cessation period increases.

These findings are shown in Table 2, which has been derived from Doll's report (7). The lung cancer death rate among men in England and Wales increased from 1.49 per 1,000 in the period 1954-57 to 1.86 per 1,000 in the period 1962-64, a rise of 25 percent. At the same time, the lung cancer death rate for British physicians dropped from 1.09 per 1,000 in the first period to 0.76 per 1,000 in the second period, a reduction of 30 percent. This reduction in death rates from lung cancer among all physicians is larger than would have been anticipated from examining only the experience of those physicians who had stopped smoking before the study began and indicates that the experience of ex-smokers in prospective studies probably understates the benefits of giving up smoking.

With these findings the case for cigarette smoking as the principal cause of lung cancer is overwhelming. The reduction of rates experienced in ex-smokers as compared with continuing smokers is clearly shown in the case of lung cancer to be a reflection of a significant change in risk. Since the concern that selective bias might have accounted for the earlier findings has been contraindicated, a stronger case can now be made for interpreting reduced rates of overall mortality for those who give up smoking as also reflecting a direct alteration of risk compared to those who continue to smoke.

There are no adequate data to evaluate the benefit of reductions in exposure that are more modest than those achieved by complete cessation, although it seems reasonable to assume that a substantial reduction in exposure is likely to be accompanied by some reduction in risk relative to those who do not reduce their exposure.

TABLE 2.—*Changes in the lung cancer death rate in male British physicians (age 35–84) compared with changes in the rates for the male population of England and Wales for 3 time intervals between 1954 and 1964 (7)*

Time period	Lung cancer death rates per 1,000 per year	
	Men in England and Wales	British physicians
1954 to 1957.....	1.49	1.09
1958 to 1961.....	1.71	.83
1962 to 1964.....	1.86	.76
Percentage change:		
1st to 2nd period.....	+15	–24
2nd to 3rd period.....	+9	–8
1st to 3rd period.....	+25	–30

Smoking and Overall Morbidity

AT THE TIME of the Surgeon General's 1964 Report there was no information available on the overall disability associated with smoking. To investigate the relationship between smoking and morbidity, the National Center for Health Statistics of the Public Health Service introduced questions about cigarette smoking into its National Health Survey, beginning in July 1964. This Survey is a continuing study conducted since 1957.

In carrying on this Survey, interviewers each year visit 42,000 families (selected as a probability sample of the civilian, noninstitutional population of the United States) and question them about illness, disability, and days absent from work because of illness, as well as the nature of the illness. In the year ending in June 1965, they inquired (after all other questions about health had been asked) about the smoking habits of persons in the family who were 17 years of age or over.

The National Health Survey is concerned with three overall measures of the impact of illness.

1. *Days Lost From Work.*—These are days absent from job or business because of illness or injury. They apply only to those persons who are currently employed and are therefore heavily concentrated in age groups 17-64.

2. *Bed Days.*—These are days when the person is sufficiently ill or disabled so as to spend all or most of the day in bed, either at home or in a hospital. All days spent as a hospital patient are included.

3. *Days of Restricted Activity.*—These are days when a person cuts down his usual activities for most of a day because of an illness or an injury. Days lost from work because of illness and bed days are, of course, counted as days of restricted activity. This represents the most general measure of disability available in the United States today.

Table 3 summarizes the findings in a form similar to that used for summarizing the overall mortality utilizing three measures of morbidity effect: Morbidity ratios, differences in rates, and excess days of disability.

TABLE 3.—Comparison of 3 measures of relationship between cigarette smoking and 3 types of disability days by age and sex as derived from the National Health Survey (16)

	Male			Female		
	17-44	45-64	65 and over	17-44	45-64	65 and over
WORK-LOSS DAYS						
Estimated total days (millions)-----	112	127	21	80	55	4
Rate: ¹						
Never smoked cigarettes-----	3.4	5.6	9.8	4.5	5.3	5.0
History of cigarette smoking----	4.4	8.5	9.8	6.5	6.9	(?)
Morbidity ratio ² -----	1.3	1.5	1.0	1.4	1.3	(?)
Difference in morbidity rates ^{1 4} -----	1.0	2.9	0	2.0	1.6	(?)
Excess days as percentage of total ⁵ —	20	28	0	18	11	(?)
RESTRICTED ACTIVITY DAYS						
Estimated total days (millions)-----	305	386	271	543	469	395
Rate: ¹						
Never smoked cigarettes-----	7.5	15.0	32.9	13.3	22.6	40.1
History of cigarette smoking----	10.6	22.9	37.9	17.8	25.3	44.8
Morbidity ratio ² -----	1.4	1.5	1.2	1.3	1.1	1.1
Difference in morbidity rates ^{1 4} -----	3.1	7.9	5.0	4.5	2.7	4.7
Excess days as percentage of total ⁵ —	23	28	8	14	5	2
BED DAYS						
Estimated total days (millions)-----	111	118	100	210	168	146
Rate: ¹						
Never smoked cigarettes-----	2.7	4.6	13.4	5.4	8.0	15.1
History of cigarette smoking----	3.9	6.9	13.0	6.7	9.2	15.2
Morbidity ratio ² -----	1.4	1.5	.97	1.2	1.1	1.0
Difference in morbidity rates ^{1 4} -----	1.2	2.3	-0.4	1.3	1.2	0.1
Excess days as percentage of total ⁵ —	23	28	-1	10	6	0

¹ Rate is defined as "days per person per year."

² Based on too few smokers for stable rates.

³ Morbidity Ratios—Morbidity rate for cigarette smokers divided by morbidity rate for those who never smoked cigarettes.

⁴ Difference in Morbidity Rates—Morbidity rate for cigarette smokers minus morbidity rate for those who never smoked cigarettes.

⁵ Excess deaths among cigarette smokers (i.e., additional days of disability that occur among cigarette smokers per year above those which would have occurred if smokers had the same rates as those who never smoked cigarettes). This is expressed as a percentage of all disability days occurring in that age-sex group.

DAYS LOST FROM WORK

For those with a history of cigarette smoking, classified by heaviest amount smoked, the average number of days was 7 percent higher for men and 15 percent higher for women who had smoked less than 11 cigarettes per day; 33 percent higher for men and 60 percent higher

for women who had smoked 11-20 cigarettes per day; 48 percent higher for men and 79 percent higher for women who had smoked 21-40 cigarettes per day; and 83 percent higher for men and 140 percent higher for women who had smoked more than 40 cigarettes per day. The relationships expressed by all three measures are somewhat higher among men aged 45-64 than among men aged 17-44, but lower among women aged 45-64 than among women aged 17-44. In the survey year, there were an estimated 399 million workdays lost in the United States because of illness. A total of 77 million days, or 19 percent, were excess workdays lost because of the higher rates which exist among persons who have ever smoked cigarettes as compared to those who never smoked. This excess loss is highest in men 45-64 where it represents 28 percent of all days lost.

BED DAYS

For those with a history of cigarette smoking, classified by heaviest amount smoked, the average number of days was 10 percent higher for men and 4 percent lower for women who had smoked less than 11 cigarettes per day; 22 percent higher for men and 17 percent higher for women who had smoked 11-20 cigarettes per day; 22 percent higher for men and 57 percent higher for women who had smoked 21-40 cigarettes per day; and 53 percent higher for men and 192 percent higher for women who had smoked more than 40 cigarettes per day. Relationships with smoking are higher for men than for women for all three measures except for age 17-44 in which the differences in morbidity rates between smokers and nonsmokers are about the same. For the entire population 17 years of age and older there were an estimated 853 million bed-days in the survey year. A total of 88 million of these days, or 10 percent, were "excess" days lost because of the higher rates which exist among persons who have ever smoked cigarettes as compared to those who never smoked. Excess days as a percentage of total bed-days is highest for men aged 45-64, where it is 28 percent.

DAYS OF RESTRICTED ACTIVITY

For those with a history of cigarette smoking classified by heaviest amount smoked, the average number of days was 12 percent higher for men and 4 percent higher for women who had smoked less than 11 cigarettes per day; 32 percent higher for men and 22 percent for women who had smoked 11-20 cigarettes per day; 39 percent higher for men and 48 percent higher for women who had smoked 21-40 cigarettes per day; and 81 percent higher for men and 146 percent higher for women who had smoked more than 40 cigarettes per day. Again rates are higher for men than for women in all three measures except for age group 17-44, in which differences in morbidity rates are higher for women. There were an estimated 2,369 million such days

in the survey year; 306 million, or 13 percent, were excess days lost because of the higher rates which exist among persons who have ever smoked cigarettes as compared to those who never smoked. Excess days as a percentage total restricted activity days was highest in men aged 45-64.

To help evaluate these general indices of morbidity as measured by various kinds of disability days it is necessary to turn to the conditions which are reported more frequently by cigarette smokers than by non-smokers. Since these are either self-reports or reports made by a responsible member of the household for others in the household, the diagnostic accuracy of the reports is obviously less than one could obtain from direct medical examination. Nevertheless, the bulk of the reports on chronic conditions reflect what a physician has previously told the patient or the family with regard to a diagnosis of the condition.

Chronic conditions (one or more) are reported by 11 percent more of the men and 9 percent more of the women who have ever smoked cigarettes than by those who have never smoked cigarettes. This is especially high in those who have reported their highest consumption rate to have been over two packs a day (32 percent higher for men and 43 percent higher for women). At the lower levels of consumption the rates reported are 21 percent and 25 percent higher for those smoking 21-40 cigarettes per day, but only 6 percent higher for men and 7 percent higher for women for those smoking 11-20 cigarettes per day and only 1 percent higher for both men and women who have never smoked more than 10 cigarettes per day. The differences are especially marked among present smokers of more than two packs per day whose rate of reporting three or more chronic conditions is 73 percent higher for men and 143 percent higher for women than for those who have never smoked cigarettes.

Applying differences in prevalence rates to the entire U.S. population 17 years of age and over yields the estimate that there are approximately 11 million more cases of chronic illness annually than there would be if all people had the same rate of sickness as those who had never smoked cigarettes. A large portion of these are accounted for by conditions classified as "chronic bronchitis and emphysema," "heart conditions," "peptic ulcers," and "sinusitis." All but the last of these have previously shown substantially higher mortality rates among cigarette smokers. Sinusitis, being a nonfatal condition, has not been identified in the studies of mortality previously reported. The "heart condition" relationship is most marked in the category "arteriosclerotic heart disease including coronary disease."

The age-adjusted incidence rate of acute conditions for persons who had ever smoked was 14 percent higher among men and 21 percent higher among women than the rates for "never smokers." However,

particular caution must be taken in interpreting the results relating specific acute conditions to cigarette smoking because of the relatively large sampling error connected with the estimates for the several types of acute conditions.

Since the National Health Survey is not a prospective study, it does not identify the rate at which various types of morbidity develop in comparable groups of smokers and nonsmokers, but reports the recent existence of such disability. Therefore, the findings are much more significant when they support relationships previously identified than when new relationships are identified. It should not be surprising that causes of mortality which are associated with cigarette smoking have a counterpart in disease or disability associated with smoking.

As the primary source of data in the United States on disability, the Survey report, being based on a national probability sample, provides a solid base for estimating the excess overall disability associated with cigarette smoking.

HIGHLIGHTS OF CURRENT INFORMATION ON OVERALL MORTALITY AND MORBIDITY

1. The previous conclusions with respect to the association between smoking and mortality are both confirmed and strengthened by the recent reports. The added period of followup and analysis of deaths of nonrespondents as well as of respondents in the Dorn Study suggests that the earlier reports may have understated the relationship.

2. More information is now available for specific age groups than previously. A comparison of three ways of measuring the relationship indicates that cigarette smoking is most important among men aged 45 to 54 both in terms of mortality ratios and excess deaths expressed as a percentage of total deaths. Nevertheless, although both of these measures decline with advancing age, the increment added to the death rate, which reflects one's personal chances of being affected, continues to increase with age. For men between the ages of 35 and 59, the excess deaths among current cigarette smokers account for one out of every three deaths at these ages. For women, with their lower overall exposure to cigarettes, the comparable figure is about one death out of every 14 at ages 35 to 59.

3. Women who smoke cigarettes show significantly elevated death rates over those who have never smoked regularly. The magnitude of the relationship varies with several measures of dosage. By and large the same overall relationships between smoking and mortality are observed for women as had previously been reported for men, but at a lower level. Not only are the death rates for men who have never smoked regularly higher than those for women who have never smoked

regularly, but the effect of smoking as measured either by differences in death rates or by mortality ratios is greater for men than for women. At least part of this can be accounted for by the lower exposure of female cigarette smokers whether measured by number of cigarettes, duration of smoking, or degree of inhalation.

4. Previous findings on the lower death rates among those who have discontinued cigarette smoking are confirmed and strengthened by the additional data reviewed. Kahn's analysis of ex-smokers in the U.S. veterans study—controlling for age at which they began smoking, amount smoked, and current age—reveals a downward trend in risk relative to those who continued to smoke as the duration of time discontinued increases. The British physician study, in which a downward trend is reported in lung cancer death rates for the entire group (smokers, ex-smokers, and those who never smoked, combined) along with a very sharp reduction in cigarette smoking by the physicians, is the best available example of a controlled cessation experiment with reduction of risks resulting from reduction of smoking. The findings of this report support the view that epidemiological data showing lower death rates among former smokers than among continuing smokers cannot be dismissed as due to selective bias and that the benefits of giving up smoking have probably been understated.

5. Cigarette smokers have higher rates of disability than non-smokers, whether measured by days lost from work among the employed population, by days spent ill in bed, or by the most general measure—days of "restricted activity" due to illness or injury. Data from the National Health Survey provide a base for estimating that in 1 year in the United States an additional 77 million man-days were lost from work, an additional 88 million man-days were spent ill in bed, and an additional 306 million man-days of restricted activity were experienced because cigarette smokers have higher disability rates than nonsmokers. For men age 45 to 64, 28 percent of the disability days experienced represent the excess associated with cigarette smoking.

Smoking and Cardiovascular Diseases

CONCLUSIONS OF THE SURGEON GENERAL'S 1964 REPORT

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

CURRENT INFORMATION, 1967

Important additional epidemiological information from five prospective mortality studies confirms that cigarette smokers have substantially higher death rates from coronary heart disease than do nonsmokers. This is true for both men and women although the relationships are less marked in women. Cigarette smoking also markedly increases an individual's susceptibility to earlier death from coronary disease. In general, mortality rates increase with increasing amounts smoked.

Cessation of cigarette smoking is followed by a reduction in the risk of coronary heart disease mortality relative to those who continued to smoke. Epidemiological evidence indicates that there is little risk of coronary heart disease associated with cigar and/or pipe smoking.

The Surgeon General's 1964 Report indicated a median mortality ratio of 1.7 for current cigarette smokers, with a range from 1.5 to 2.0. Additional evidence from the Hammond study (11) indicates that young smokers between the ages of 45 and 54 have the highest mortality ratios—three times as great for men, and twice as great for women if they smoke 10 or more cigarettes per day, as compared with nonsmokers. In general, the mortality ratio shows the most marked increases with increasing amount smoked for the ages under 65. While the cigarette smokers older than 65 have lower mortality ratios than those under 65, the public health significance of the relationship in the older population is substantial because of the large numbers of people over 65 who die of coronary heart disease. Studies of U.S. veterans (13), Canadian pensioners (1), British physicians (8, 9, 10),

and California longshoremen (3) also provide extensive additional information about coronary heart disease in male cigarette smokers as compared to nonsmokers, supporting the above statements as they pertain to men.

The study of British physicians (8, 9, 10) suggests that male cigarette smokers have the largest increase in risk for death certified to coronary thrombosis—a subcategory of coronary heart disease describing acute coronary events, frequently occlusive, causing myocardial infarction. For that subcategory, the mortality ratio is also largest for the younger age groups 35–54.

Prospective morbidity studies confirm the relationships between cigarette smoking and coronary heart disease. These studies also provide the opportunity to evaluate the effect of smoking independently and in combination with other known “risk factors,” such as high blood pressure and high serum cholesterol that are also important in the pathogenesis of coronary heart disease. It has been demonstrated that cigarette smoking not only operates as an independent “risk factor” but that it may combine with other “risk factors” to produce even greater effects on cardiovascular health.

Other types of evidence have also been presented to confirm the epidemiologic evidence. Autopsy studies show that cigarette smokers have a much greater frequency of advanced coronary arteriosclerosis than do nonsmokers. Clinical and experimental studies demonstrate that smoking produces abnormalities of cardiovascular physiology that may help to explain the mechanisms of how smoking may produce earlier death from coronary heart disease.

Human and experimental studies indicate that the nicotine absorbed from smoking may cause an increase in the myocardial tissue demand for oxygen yet at the same time the carbon monoxide absorbed from smoking may cause a decrease in the supply of available oxygen from the blood necessary to meet the increased myocardial tissue demand. Studies indicate that some persons who already have pre-existing coronary heart disease, not necessarily clinically obvious, may be especially susceptible to the adverse physiological effects of smoking. Evidence also indicates that important differences may exist between normal individuals and those with coronary heart disease in their ability to increase coronary blood flow to compensate for increased myocardial tissue oxygen demand. Smoking apparently can accelerate thrombus formation of human blood, suggesting another possible mechanism whereby smoking might increase the mortality from coronary heart disease, especially those acute coronary events certified as “coronary thrombosis.”

The convergence of many types of evidence—epidemiological, experimental, pathological, and clinical—strongly suggests that cigarette smoking can cause death from coronary heart disease. These

biomechanisms may help to explain why cigarette smokers have such an increased risk of developing coronary heart disease and of dying from it.

An increasing amount of evidence has been accumulated in the past few years relating the development of clinical cerebrovascular disease to cigarette smoking. Most of this information has come from mortality studies (17, 18), both retrospective and prospective, which show that both male and female smokers of cigarettes under the age of 75, as compared to nonsmokers, have higher death rates from cerebrovascular disease designated as the underlying cause of death on their death certificates. This may be especially true for younger cigarette smokers age 45-54 where males had death rates about 50 percent higher than nonsmoking males, and females had death rates about 100 percent higher than nonsmoking females. Under age 75, mortality ratios for stroke increase as the number of cigarettes smoked increases. No association has been shown for those aged 75 and over.

The new epidemiological evidence, then, indicates that cigarette smoking may be more closely associated with cerebrovascular disease than previously indicated in the population between the ages of 45 and 74 years. If cerebrovascular thrombosis (thrombotic brain infarction) accounts for this association, it is possible that some of the considerations of how cigarette smoking may produce coronary thrombosis also apply to the pathogenesis of cerebrovascular disease. Further research is essential to understand the relationships which exist between cigarette smoking and cerebrovascular disease.

Additional epidemiological evidence from prospective mortality studies provides confirmation that cigarette smoking is associated with increased death rates from aortic aneurysm (nonsyphilitic), for both men and women. In one study of male smokers an increase in death rates was noted with increases in amount smoked.

HIGHLIGHTS OF CURRENT INFORMATION

1. Additional evidence not only confirms the fact that cigarette smokers have increased death rates from coronary heart disease, but also suggests how these deaths may be caused by cigarette smoking. There is an increasing convergence of many types of evidence concerning cigarette smoking and coronary heart disease which strongly suggests that cigarette smoking can cause death from coronary heart disease.

2. Cigarette smoking males have a higher coronary heart disease death rate than nonsmoking males. This death rate may, on the average, be 70 percent greater, and, in some, even 200 percent greater or

more in the presence of other known "risk factors" for coronary heart disease. Female cigarette smokers also have higher coronary heart disease death rates than do nonsmoking females, although not as high as that for males. In general, the death rates from this disease increase with amounts smoked. Cessation of cigarette smoking is followed by a reduction in the risk of dying from coronary heart disease when compared with the risk incurred by those who continue to smoke.

3. A greater frequency of advanced coronary arteriosclerosis is noted in male cigarette smokers, especially in those who smoke heavily.

4. Additional evidence strengthens the association between cigarette smoking and cerebrovascular disease, and suggests that some of the pathogenetic considerations pertinent to coronary heart disease may also apply to cerebrovascular disease.

Smoking and Chronic Bronchopulmonary Diseases (Non-Neoplastic)

CONCLUSIONS OF THE SURGEON GENERAL'S 1964 REPORT

1. 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.

2. 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.

3. 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.

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

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

6. Cigarette smoking does not appear to cause asthma.

7. 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.

CURRENT INFORMATION, 1967

Additional evidence from the four major prospective studies indicates that cigarette smokers have a markedly increased risk of dying from chronic bronchitis and pulmonary emphysema. The range of risk varies for cigarette smokers between three and 20 times the mortality rates for nonsmokers, and depends in part on the total amount smoked and the age group studied. Female cigarette smokers have similarly increased mortality risks although somewhat lower than those for males. Cessation of cigarette smoking is followed by a lower mortality risk relative to those who continue to smoke. Generally, pipe

and cigar smokers are much less affected than cigarette smokers by these diseases.

Problems of nomenclature and diagnosis make satisfactory differentiation of chronic bronchitis from pulmonary emphysema difficult when considering the epidemiologic data. Nevertheless autopsy studies support the relationship between smoking and mortality. In addition, recent information from morbidity studies indicates that smoking is associated with symptoms of chronic bronchopulmonary disease. Even relatively young cigarette smokers show increased respiratory symptoms and decreased ventilatory function. Cessation of smoking is usually followed by improvement of these characteristics. Although some individuals may have an increased susceptibility to respiratory disease, studies of twin-pairs in Sweden (4, 5, 6, 14)—in which one twin is a smoker and the other is not—show that those who smoke have a much greater frequency of respiratory symptoms and abnormalities of ventilatory function than do their nonsmoking twins. This demonstrates that cigarette smoking is of greater importance than hereditary and constitutional factors in the pathogenesis of chronic bronchopulmonary disease. Similarly, occupational exposures and air pollution may also cause respiratory disease, but cigarette smoking is of much greater importance.

Additional clinical and experimental laboratory evidence confirms the fact that constituents in tobacco smoke are harmful to the bronchial mucosa of the respiratory tract. Bronchial changes have been produced in experimental animals exposed to cigarette smoke.

It is suspected that smoking has a direct toxic effect upon the alveolar tissue of human lungs, in which case this effect might be important in the pathogenesis of many though not all cases of human pulmonary emphysema. Additional indirect evidence exists to substantiate this suspected toxic effect, but additional research is needed to confirm or deny the presence of the effect. However, the presently available evidence (epidemiological, clinical, pathological, and experimental) strongly suggests that cigarette smoking may well play an important pathogenic role in many, although not necessarily all, cases of pulmonary emphysema. The fact that other causes of pulmonary emphysema exist does not detract from the validity of this inference.

Additional evidence strongly supports the conclusion in the Surgeon General's 1964 Report that 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.

HIGHLIGHTS OF CURRENT INFORMATION

1. New data confirm and to some extent strengthen the conclusions of the Surgeon General's 1964 Report.
2. Cigarette smoking is the most important of the causes of chronic non-neoplastic bronchopulmonary diseases in the United States. It greatly increases the risk of dying not only from both chronic bronchitis but also from pulmonary emphysema.
3. Cessation of smoking is followed by a reduction in mortality from chronic bronchopulmonary disease relative to the mortality of those who continue to smoke.
4. Even relatively young cigarette smokers frequently have demonstrable respiratory symptoms and reduction in ventilatory function.

Smoking and Cancer

CONCLUSIONS OF THE SURGEON GENERAL'S 1964 REPORT

Lung Cancer

1. 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.

2. 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.

3. 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 nonsmokers, but much less than for cigarette smokers. The data are insufficient to warrant a conclusion for each group individually.

Oral Cancer

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

2. 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.

Laryngeal Cancer

Evaluation of the evidence leads to the judgment that cigarette smoking is a significant factor in the causation of laryngeal cancer in the male.

Esophageal Cancer

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.

Cancer of Urinary Bladder

Available data suggest an association between cigarette smoking and urinary bladder cancer in the male but are not sufficient to support judgment on the causal significance of this association.

Stomach Cancer

No relationship has been established between tobacco use and stomach cancer.

Additional chemical, experimental, pathological, and epidemiological evidence has been reported that substantiates the conclusions of the Surgeon General's 1964 Report concerning the various sites of cancer that were shown to be associated with or caused by smoking.

LUNG CANCER

Deaths from lung cancer in the United States are continuing to rise rapidly. Epidemiological evidence concerning cigarette smoking and lung cancer has confirmed positive relationships with increasing numbers of cigarettes smoked, with increasing duration, and with decreasing age of initiation of the habit. Male cigarette smokers of less than one pack a day have mortality ratios as high as 10 and smokers of more than one pack a day have mortality ratios as high as 30.

There is a much smaller increase of the lung cancer death rates associated with pipe and/or cigar smoking than with cigarette smoking.

Additional evidence provides specific information on the increased mortality ratios of female cigarette smokers. These have significantly elevated mortality ratios ranging as high as 5 for the groups with greatest exposure. Lung cancer rates appear to be somewhat lower for women who have never smoked regularly than for men who have never smoked regularly. The mortality rates for women who smoke, although significantly higher than for nonsmokers, are lower than for men who smoke. How much of this is due to lower exposure to cigarettes and how much to other factors cannot be determined from the data available.

Ex-cigarette smokers are shown to have significantly lower death rates compared with those who continue to smoke. As discussed under the general topic of cessation earlier in this report, the finding of reduced lung cancer rates in the population of British physicians (8, 9, 10) over a period of time in which the proportion of cigarette smokers was dropping significantly can be interpreted as similar to a controlled cessation experiment and provides critical confirmation of the judgment that cigarette smoking is the major cause of lung cancer and that sharp reductions can occur in the risk from lung cancer with the cessation of smoking.

Additional information is available concerning the presence of known or suspected carcinogens in tobacco smoke. It has been reported that the "tar" and nicotine content of cigarette smoke* tends to reflect the tumorigenicity of this smoke, and that a reduction of the "tar" and

* The phrase "tar" and nicotine" is used here as a general indicator of total particulate matter in cigarette smoke.

nicotine content is accompanied by a reduction in the tumorigenicity. Research is needed to identify and separate the tumor-initiating and tumor-promoting agents in tobacco smoke and to elucidate their interactions in the pathogenesis of cancer. Similarly, while additional data are available concerning experimental carcinogenesis, it is not yet certain that the typical characteristics of human squamous-cell lung cancer, with invasion and metastasis, have been experimentally produced by tobacco smoke in animals. It should be noted that this may never be achieved not only because it may not be possible to duplicate man's smoking action for anatomic and physiologic reasons but also because of species' differences in cellular response.

There is evidence that certain other exposures, for example, occupational exposures to asbestos and uranium ore may interact with the cigarette effect to produce an enhancement of the tumor-producing effect. There is also information to indicate that the occurrence of second primary lung cancers in smokers may be more frequent than previously indicated.

ORAL CANCER

Substantial mortality ratios are found for cancers of the buccal cavity and pharynx. Mortality ratios for cancer of the pharynx are especially high. There is some evidence implicating alcohol and/or dietary deficiencies in some of these sites. With the exception of the pipe-lip cancer relations there are too few cases related to the individual parts of the buccal cavity to evaluate each independently, and data are inadequate on the interaction of smoking with other factors. Although all forms of smoking have high mortality ratios with these sites, mortality ratios for those smoking cigarettes appear to be somewhat higher than for those smoking pipes and cigars, especially in the case of cancer of the pharynx.

LARYNGEAL CANCER

Continued evidence from the prospective studies supports the existence of a high laryngeal cancer mortality ratio for pipe and cigar smokers as well as for cigarette smokers. Data on the smoking habits of patients treated for buccal cancer subsequent to their therapy suggests that continuing to smoke after therapy may increase the likelihood of an independent laryngeal cancer. The epidemiological evidence supports the previous conclusion that cigarette smoking is a significant factor in the causation of cancer of the larynx.

ESOPHAGEAL CANCER

Additional data from the prospective studies confirm the high mortality ratio previously found for smokers of all forms of tobacco.

Autopsy studies of smokers compared with nonsmokers specifically observing pathological changes in esophageal tissue have been reported from both smokers and nonsmokers who died from causes other than esophageal cancer. The findings were similar to the abnormalities generally accepted as representing premalignant tissue changes of the epithelium of the respiratory tract; that is, epithelial cells with atypical nuclei were found far more frequently in cigarette smokers than in nonsmokers. Tissue sections with basal cell hyperplasia were also found more frequently in cigarette smokers and, as with the atypical nuclei, these findings increased with amount of cigarette smoking. Additional data to evaluate the relative importance of smoking and alcohol, independently and jointly, would help clarify the significance of these findings.

URINARY BLADDER CANCER

The Dorn (13) and the Hammond (11) studies both show mortality ratios over 2.0 for smokers of over 20 cigarettes a day, but the Doll-Hill study (8, 9), based on only 38 deaths, shows no apparent relationship. Two retrospective studies have shown significantly higher proportions of smokers among patients than among controls. Small scale metabolic studies suggest that cigarette smoking may block the normal metabolism of tryptophan, which would lead to the accumulation of carcinogenic metabolites in the urine. Further studies to verify this finding and studies analyzing changes in the bladder tissue of smokers as compared with nonsmokers would be helpful in arriving at a judgment of the significance of the elevated death rates found in smokers in the largest of the prospective studies.

STOMACH AND PANCREATIC CANCER

Epidemiological evidence does not show a significant relationship between smoking and stomach cancer. An association between cigarette smoking and pancreatic cancer is implied, but the significance of this association is not clear at the present time.

HIGHLIGHTS OF CURRENT INFORMATION

LUNG CANCER

1. Additional epidemiological, pathological, and experimental data not only confirm the conclusions of the Surgeon General's 1964 Report regarding lung cancer in men but strengthen the causal relationship of smoking to lung cancer in women.

2. Cessation of cigarette smoking sharply reduces the risk of dying from lung cancer relative to the risk of those who continue.

3. Although additional experimental studies substantiate previous experimental data, additional research is needed to specify the tumor-initiating and tumor-promoting agents in tobacco smoke and to elucidate the basic mechanisms of the pathogenesis of lung cancer.

LARYNGEAL CANCER

The conclusion of the Surgeon General's 1964 Report that cigarette smoking is a significant factor in the causation of laryngeal cancer in the male is supported by additional epidemiological evidence.

OTHER CANCERS

Additional evidence supports the conclusions of the Surgeon General's 1964 Report and indicates a strong association between various forms of smoking and cancers of the buccal cavity, pharynx, and esophagus. In the absence of further information concerning the interaction of smoking with other factors known or suspected as causative agents, further conclusions cannot be made at this time, although a causative relationship seems likely.

Additional epidemiological, clinical, and experimental data strengthen the association between cigarette smoking and cancer of the urinary bladder, but the presently available data are insufficient to infer that the relationship is causal.

Other Conditions and Areas of Research

CONCLUSIONS OF THE SURGEON GENERAL'S 1964 REPORT

Peptic Ulcer

Epidemiological studies indicate an association between cigarette smoking and peptic ulcer which is greater for gastric than for duodenal ulcer.

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.

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 casual association.

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.

Psychosocial Aspects

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 heredity factors.

CURRENT INFORMATION, 1967

By and large the contributions to knowledge in this area of varied considerations have been meager, although a number of investigations

on one or another aspect of the problem of smoking and varied health consequences have been undertaken.

PEPTIC ULCER

The relationship between cigarette smoking and death rates from peptic ulcer, especially gastric ulcer, is confirmed. In addition, morbidity data suggest a similar relationship exists with the prevalence of reported disease from this cause.

TOBACCO AMBLYOPIA

Tobacco amblyopia is now believed to be a manifestation of nutritional amblyopia, which is aggravated by the inhalation of tobacco smoke. Various vitamin B factor deficiencies may be involved and there is evidence to suggest that chronic low vitamin B₁₂ levels may potentiate the toxic effects of cyanide in tobacco smoke.

CIRRHOSIS OF THE LIVER

Increased mortality of smokers from cirrhosis of the liver is found in the prospective studies. This has generally been thought to be largely secondary to an association between smoking and heavy consumption of alcohol. Published data are inadequate to test this interpretation.

MATERNAL SMOKING AND INFANT BIRTH WEIGHT

Further studies have confirmed the fact that women who smoke during pregnancy tend to have babies of lower birth weight, but data are lacking to determine either the mechanism or the significance of this finding.

PSYCHOSOCIAL ASPECTS

There has been a sharp increase in the attention devoted to behavioral research since the Surgeon General's Report. A number of new concepts have been developed and more sophisticated multivariate approaches are being used. However, because of the recency of these studies very little in the way of findings has been published on which firm conclusions may be based.

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PART II

Technical Reports on the Relationship of Smoking to Specific Disease Categories

CHAPTER 1

Smoking and Cardiovascular Diseases

CONTENTS

	Page
Smoking and Coronary Heart Disease.....	47
Coronary Heart Disease Mortality.....	47
Coronary Heart Disease Morbidity.....	53
Manifestations of Coronary Heart Disease.....	58
Cardiovascular Response to Smoking and/or Nicotine....	60
Coronary Blood Flow in Normal Subjects.....	60
Coronary Blood Flow in Subjects With Coronary Heart Disease.....	61
Carbon Monoxide Effect.....	62
Studies on <i>In Vitro</i> Thrombus Formation.....	64
Autopsy Studies.....	65
Smoking and Cerebrovascular Disease.....	66
Smoking and Aortic Aneurysm.....	69
Cited References.....	69
Supplemental References.....	76

SMOKING AND CORONARY HEART DISEASE

CORONARY HEART DISEASE MORTALITY ¹

The relative importance of the association between cigarette smoking and coronary heart disease (CHD) as compared to the association of smoking with other diseases was previously described in the introduction to chapter 11 of the Surgeon General's 1964 Report.

In the United States more persons die from coronary heart disease than from any other single cause; and this most common form of fatal cardiovascular disease accounts for a greater percentage of excess deaths among cigarette smokers than do deaths from lung cancer. In 1964, there were 1,798,000 deaths from all causes, of which almost 545,500 or 30.3 percent, were due to atherosclerotic heart disease, including coronary heart disease. Table 1 gives the 1964 death rates for coronary heart disease per 100,000 persons by age and sex:

TABLE 1.—1964 death rates for coronary heart disease per 100,000 persons by age and sex

	All ages	25-34	35-44	45-54	55-64	65-74	75-84	85+
Both Sexes..	285. 1	6. 9	53. 2	205. 8	576. 3	1, 384. 9	2, 957. 7	6, 882. 9
Males.....	354. 2	11. 0	90. 9	341. 3	889. 8	1, 942. 4	3, 623. 0	7, 409. 4
Females....	218. 5	3. 0	17. 4	76. 8	286. 4	926. 5	2, 464. 0	6, 559. 0

SOURCE: National Center for Health Statistics (97).

These data illustrate the dramatic increases in the risk of death from coronary heart disease as age advances. For males the rates among persons over the age of 45 appear to double from one decade to the next; among females the increased risk of death with advancing age is more dramatic—a threefold increase every 10 years. Of perhaps greater importance are the relatively low death rates among females, particularly below the age of 65, compared to males of comparable age. The mortality differential between the sexes becomes less as age advances; under 45 years of age the coronary death rate among men is five times as high as among women and in the 75-84 year age group it is only about 1.5 times as high.

The Surgeon General's 1964 Report determined a median mortality ratio (99) (pp. 109-110) for coronary heart disease of male current cigarette smokers of 1.7. Since this report, five large prospective

¹All death rates throughout this chapter are per 100,000 population, unless otherwise indicated.

studies of smoking and mortality have been updated on the basis of longer periods of observation on each study subject. Current findings are therefore more definitive and permit more detailed analysis of the interrelationship of cigarette smoking to other significant variables such as age, sex, and the nature of the smoking habit in terms of amount and duration of smoking. Pertinent findings are presented below from the studies of veterans in the United States (52) and Canada (14) and the extensive data reported by Hammond (47), Doll and Hill (25, 26, 27), and Borhani (17).

The relative excess mortality associated with cigarette smoking is generally expressed in terms of a mortality ratio. This statistic is defined as the ratio of the number of observed deaths among smokers, to the expected deaths among smokers, if the age-specific mortality rates observed among non-smokers had prevailed (52). The process of computing the expected number of deaths among smokers takes into account and adjusts for any differences in the age distribution of the smokers and the nonsmokers under observation. Generally smokers are defined as persons currently smoking cigarettes, and non-smokers as those who never smoked or who never smoked regularly.

Table 2 shows the mortality ratios for coronary heart disease deaths among current cigarette smokers according to the amount smoked daily in U.S. and Canadian male veterans.

TABLE 2.—*Coronary heart disease mortality ratios, age-adjusted among current cigarette smokers by amount smoked daily*

	Cigarettes smoked daily				
	Under 10	10-20	21-39	More than 20	40+
U.S. male veterans.....	1.3	1.7	1.8	-----	2.0
Canadian male veterans.....	1.6	1.6	-----	1.8	-----

SOURCE: U.S. veterans study (52) and Canadian pensioners study (14).

In both studies (14, 52) the mortality ratios were similar and increased with increasing intensity of cigarette smoking. Slightly higher ratios are reported in the U.S. veterans study for current smokers of cigarettes only.

The U.S. veterans study also permitted the comparison of age-specific coronary heart disease mortality rates for ex-smokers and current cigarette smokers (table 2A). From these data, it appears that cessation of cigarette smoking is followed by a reduction in risk of coronary heart disease mortality as compared to those who continue to smoke cigarettes.

TABLE 2A.—Annual death rate per 100,000 from coronary heart disease by age, cigarette-smoking status and number of cigarettes smoked per day, U.S. veterans study

Number smoked per day ¹	45-54		55-64		65-74	
	Current cigarette smokers	Ex-smokers ²	Current cigarette smokers	Ex-smokers ²	Current cigarette smokers	Ex-smokers ²
1 to 9.....	195	125	594	432	1,374	1,105
10 to 20.....	297	133	830	557	1,577	1,260
21 to 39.....	390	57	912	743	1,701	1,366
40+.....	502	-----	1,101	646	1,955	1,482

¹ This is the current rate of smoking for current cigarette smokers and the maximum rate attained for ex-cigarette smokers.

² Ex-smokers who stopped for reasons other than doctor's orders.

SOURCE: U.S. veterans study (58).

The Hammond study findings summarized in table 3 are based on coronary heart disease deaths reported over a 4-year period among approximately 1 million persons (441,000 men and 563,000 women).

TABLE 3.—Coronary heart disease mortality ratios among current cigarette smokers only, by amount smoked daily

Age and sex	Non-smokers	Cigarettes smoked daily			
		Under 10	10-19	20-39	40+
Men:					
45 to 54.....	1.0	2.4	3.1	3.1	3.4
55 to 64.....	1.0	1.5	1.9	2.0	2.1
65 to 74.....	1.0	1.3	1.6	1.6	(¹)
75 to 84.....	1.0	1.2	1.4	1.1	-----
Women:					
45 to 54.....	1.0	0.9	2.0	2.7	-----
55 to 64.....	1.0	1.3	1.6	2.0	-----
65 to 74.....	1.0	1.1	1.4	1.9	-----
75 to 84.....	1.0	-----	-----	-----	-----

¹ Expected deaths were less than 10.

SOURCE: Hammond, E. C. (47).

Tables 3 and 4 show that both men and women who smoke cigarettes have relatively higher death rates from coronary heart disease than nonsmokers, although men have higher rates than women. For each sex and for each age group, the mortality ratios for coronary heart disease generally increase with increased intensity of cigarette smoking (table 3). The highest mortality ratios for both men and women are observed in the 45-54 year age-group; the coronary heart disease

death rates among heavy smokers in this age group are three times the death rates for nonsmokers for both sexes. The mortality ratios for both men and women decrease with advancing age in each intensity category. This trend may reflect the effects of selective survival of smokers who have survived the elevated risks at younger ages of coronary heart disease and other diseases associated with cigarette smoking.

Another explanation of the decrease in mortality ratios with aging is that the effect of smoking, while substantial in increasing death rates, cannot be expected to be proportionate to all other causes of coronary heart disease as age advances. Considering the advanced degree of atherosclerosis generally found among nonsmokers over age 65, the deleterious effect of smoking is more appropriately represented by the excess in death rates among smokers. Table 4 below shows the observed death rates from coronary heart disease among persons studied by Hammond and classified by age, sex, and smoking status. Although the mortality ratios decreased with age, differences in death rates, which reflect the numbers of persons who die in each age group, increase. This could be interpreted to mean that, although relative to other factors, the role of cigarette smoking tends to diminish with advancing age, the number of excess deaths per 100,000 smokers continues to rise with advancing age.

TABLE 4.—Age-specific death rates from coronary heart disease per 100,000 persons by age, sex, and smoking status

Age and sex	Smokers of cigarettes only	Nonsmokers	Excess rate smokers/nonsmokers ¹	Mortality ratio
Males:				
45 to 54.....	422	150	272	2.8
55 to 64.....	996	542	454	1.8
65 to 74.....	2,025	1,400	625	1.5
75 to 84.....	3,871	3,132	739	1.2
Females:				
45 to 54.....	66	33	33	2.0
55 to 64.....	275	163	112	1.7
65 to 74.....	941	653	288	1.4
75+.....	2,349	1,973	376	1.2

¹ Calculated from the data.

SOURCE: Hammond, E. C. [(47), p. 145.]

The relative decrease in death rates from coronary heart disease associated with the cessation of cigarette smoking is illustrated by table 4A.

TABLE 4A.—Coronary heart disease (men). Age-standardized death rates for ex-cigarette smokers with history of cigarette smoking only, by former number of cigarettes smoked per day and years since last cigarette smoking. Death rates for current cigarette smokers with history of cigarette smoking only and men who never smoked regularly are shown for comparison. Men aged 50-69

Ex-cigarette smokers (years since last cigarette smoking)	Smoked 1-19 cigarettes a day			Smoked 20+ cigarettes a day		
	Number of men	Number of deaths	Death rate	Number of men	Number of deaths	Death rate
Under 1 year.....	746	27	¹ 1,005	2,244	77	¹ 1,070
1 to 4 years.....	1,844	51	718	5,435	195	1,003
5 to 9 years.....	1,770	48	725	5,803	152	732
10+ years.....	4,209	84	498	8,142	206	679
Total ex-smokers.....	8,569	210	635	21,624	630	813
Current cigarette smokers.....	22,808	781	947	56,886	1,895	1,029
Never smoked regularly.....	55,728	1,114	502	55,728	1,114	502

¹ Four or more but less than 10 deaths expected in some of the component 5-year age groups.

SOURCE: Hammond, E. C. [(47), p. 148].

Doll and Hill

In a prospective study by Doll and Hill (27) of mortality among British physicians whose smoking habits had been previously recorded, there were 1,369 deaths in the course of 10 years in which the underlying cause was coronary heart disease (27, table 1). The physician population under observation totaled 320,185 person-years. The CHD deaths were classified into three major subcategories: Group 1, comprising 35 CHD deaths in which an associated condition related to smoking, e.g., lung cancer, was recorded on the death certificate; Group 2, comprising 721 CHD deaths in which no other significant contributory cause of death was recorded on the death certificate; and Group 3, comprising 613 CHD deaths which were associated with some other contributory cause, including conditions known to predispose to coronary heart disease, e.g., hypertension, diabetes, and obesity. The CHD death rates for smokers and nonsmokers based only on Group 1 deaths, while subject to large variation, show the largest differentials (data not shown). Among smokers of 25 or more cigarettes daily, the age-adjusted CHD death rate was nearly eight times that in nonsmokers.

Based on Group 2 coronary heart disease deaths, presumably uncomplicated by any other significant disease, the mortality ratio of age-adjusted death rates among continuing cigarette smokers to nonsmokers is found to be 1.6, and for heavy smokers to nonsmokers the

ratio is 2.0. However, as shown in table 5, the mortality differentials between smokers and nonsmokers are much larger at the younger ages.

TABLE 5.—Mortality ratios for different types of coronary heart disease by smoking habits

Age group	Group 2 ¹ CHD			Group 3 CHD		
	Non-smokers	Continuing cigarette smokers		Non-smokers	Continuing cigarette smokers	
		All amounts	25 or more per day		All amounts	25 or more per day
35 to 44.....	1.0	4.7	9.7	(²)	(²)	(²)
45 to 54.....	1.0	3.8	3.5	1.0	1.1	1.7
55 to 64.....	1.0	1.4	1.6	1.0	1.4	1.9
65 to 74.....	1.0	1.4	1.8	1.0	1.4	.8
75 to 84.....	1.0	1.1	2.0	1.0	.8	.2
85 plus.....	1.0	1.0	(³)	1.0	1.4	(³)
Age adjusted—All ages..	1.0	1.6	2.0	1.0	1.1	.9

¹ See text for definitions.

² Not calculable; no rate for nonsmokers because of so few deaths.

³ Very few men in this category.

SOURCE: Data in above table based on values from Study of British Physicians. Table 3 (87).

The mortality ratios shown for Group 3 deaths, i.e., CHD deaths accompanied by some other complicating disease, suggest that, for all age groups combined, smokers do not have any special risk to this type of coronary death. However, smokers below the age of 65 appear to be at a somewhat greater risk, while no consistent differentials are observed among persons in the older age groups.

In summary, the study substantiates other mortality studies' findings that CHD mortality ratios (current cigarette smokers vs. non-smokers) increase with the number of cigarettes smoked daily, that the ratios are highest in the age group 45-54, and that they decrease as age advances. Moreover, smoking apparently is associated with deaths from coronary heart disease among persons free of other serious disease states.

In a prospective study of California longshoremen, Borhani (17) reported on the mortality experience of more than 3,700 men observed for 10 years. Table 6, derived from his data, provides some additional insights on both the independent and the interaction effects of cigarette smoking.

Men 45-64 years of age who were heavy smokers experienced higher death rates from coronary heart disease than did nonsmokers independent of whether they were hypertensive or nonhypertensive.

TABLE 6.—Mortality ratio from coronary heart disease among male hypertensives and nonhypertensives by smoking history and age

Age group	Blood pressure status ¹	Non-smokers ²	Heavy smokers ²
45 to 54.....	Nonhypertensive.....	1.0	2.2
	Hypertensive.....	2.5	9.6
55 to 64.....	Nonhypertensive.....	1.0	5.8
	Hypertensive.....	5.9	9.4

¹ Hypertensives are defined as those having systolic blood pressure of 160 mm. Hg. or over or diastolic blood pressure of 95 mm. Hg. or over. Nonhypertensives have systolic blood pressure less than 160 mm. Hg. or diastolic blood pressure less than 95 mm. Hg.

² Nonsmokers in this particular study are defined as those not smoking any cigarettes or less than 20 cigarettes per day. Smokers are those who smoke 20 or more per day.

SOURCE: Borhani, N. O., et al. (17).

An analysis was made by Schor (86) of 181 adult males who died from coronary heart disease generally less than 2 years after receiving a periodic health examination. The results of this study and those of Doll and Hill suggest that sudden death from previously undetected coronary heart disease frequently occurs among cigarette smokers. If this is true, it may, in part, account for the small differentials in the prevalence of coronary heart disease between smokers and nonsmokers observed in some morbidity prevalence surveys. As will be described in the following section, longitudinal, prospective morbidity studies also show that smokers are more likely to die from sudden attacks of coronary heart disease.

CORONARY HEART DISEASE MORBIDITY*

In chapter 11 of the 1964 Surgeon General's Report, several prospective studies on the incidence of coronary heart disease (24, 31, 78, 88) established that smokers were subject to higher rates than nonsmokers. The relationship was reported to be more marked under 50 years of age than among older persons and appeared to be associated with myocardial infarction but not with angina pectoris. Since the 1964 report, recent findings from large-scale, on-going prospective studies have been reported, providing additional insight on the interaction between smoking and other important coronary heart disease risk factors. Current findings are summarized in the following pages including tables 7 to 13. Whenever possible, data are shown separately for findings related to angina pectoris and those pertaining to myocardial infarction, including sudden death attributed to coronary heart disease. Higgins (50) has drawn attention to the fact that "many factors may influence or be affected by smoking habits, and obscure those differences between smokers and nonsmokers which are directly related to the use of tobacco." In her review of the literature, Higgins identified differences between smokers and nonsmokers in genetically

*Also may include mortality data in this presentation.

determined qualities (23), in physique (77, 93), in personality (37, 47, 48, 65, 68, 69), and in social, cultural, religious, and economic characteristics (46, 49, 63, 84).

Age

The effect of age on the incidence of coronary heart disease with regard to cigarette smoking is shown in table 7 based on recent data from the Framingham Study as yet unpublished.

TABLE 7.—Incidence rates and morbidity ratios for coronary heart disease by age and smoking status of men 12-year experience, Framingham, Mass.

Age	Incidence rates per 1,000		Excess rates per 1,000	Morbidity ratio	
	Non-smokers	Smokers	Smokers minus non-smokers	Non-smokers	Smokers
35 to 44.....	1.4	4.1	2.7	1.0	2.9
45 to 54.....	4.6	11.1	6.5	1.0	2.4
55 to 64.....	16.2	25.4	9.2	1.0	1.6

Source: U.S. Public Health Service, Framingham Study (98). (Updated 1967)

When the incidence rate of coronary heart disease among male non-smokers between 35–44 years of age is compared with that among older nonsmokers, the rate is seen to triple every 10 years. This marked increase in incidence among nonsmokers reflects the effect of other important risk factors and perhaps accounts for the decrease in morbidity ratio as age advances. The independent effect of smoking on the incidence of coronary heart disease is believed to be more appropriately represented by the excess morbidity rates, which increase from 2.7 per 1,000 smokers in the age group 35–44 to 9.2 per 1,000 smokers 55–64 years of age.

High Blood Pressure

Although the inhalation of cigarette smoke is frequently accompanied by acute transient elevations in blood pressure, habitual smokers tend to have lower blood pressures than do nonsmokers (48). But, given the presence of high blood pressure in an individual, smoking acts as an additional risk factor for the development of coronary heart disease (17, 28, 29, 30, 53, 55, 95, 96). Both the independent and the combined effect of cigarette smoking is clearly shown in table 8 derived from the experience of the Framingham and Albany studies (30).

TABLE 8.—Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to level of systolic blood pressure

Systolic blood pressure	Nonsmokers of cigarettes	Cigarette smokers
Under 130 mm. Hg-----	1.0	2.1
130 mm. Hg and over-----	1.8	3.8

SOURCE: 10-year Framingham and 8-year Albany experience (30).

High Serum Cholesterol

It is not now conclusively known if cigarette smoking by itself can cause increases in serum cholesterol. Dietary influences as well as endogenous production and elimination of cholesterol must be evaluated in greater detail with simultaneous analysis of the roles of other risk factors, including smoking. One study of a small population of twins in Sweden, as reported by Lundman (67), suggests that smoking monozygotic twins tend to have lower cholesterol levels than their nonsmoking control twins, although the differences are not statistically significant. Other studies suggest that smokers generally have higher serum cholesterol than nonsmokers (13, 67, 88). However, given the presence of high serum cholesterol, smoking increases the risk of coronary heart disease (95, 96).

The independent and synergistic effect of cigarette smoking is demonstrated by the data in table 9 derived from the combined experience of the Framingham and Albany studies (30).

TABLE 9.—Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to level of serum cholesterol

Serum cholesterol level	Nonsmokers of cigarettes	Cigarette smokers
Low ¹ -----	1.0	1.8
High ¹ -----	2.0	4.5

¹ "Low" is below median, "high" is above median value of serum cholesterol.

SOURCE: 10-year Framingham and 8-year Albany experience (30).

Pulmonary Function

The acute effects of cigarette smoking upon pulmonary function are expressed mainly through increase in airway resistance. The differences in pulmonary function between smokers and nonsmokers appear to be greater than can be accounted for by acute effects from a recently smoked cigarette (50, 91). The relationship of coronary heart disease to lowered pulmonary function as reflected by low vital capacity and cigarette smoking is observed in the data published by the Na-

national Institutes of Health based on the 12-year experience in Framingham (96). Morbidity ratios derived from this publication are shown in table 10.

TABLE 10.—Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to level of vital capacity

Vital capacity	Nonsmokers of cigarettes	Cigarette smokers
Under 3 liters.....	1.0	1.7
3 liters or more.....	1.7	2.4

SOURCE: The Framingham heart study. (96).

Here again, the independent and combined effects of cigarette smoking are observed.

Physical Inactivity

A physically inactive or sedentary individual seems to run a higher risk of developing coronary heart disease (39, 40, 41, 76). Spain (88) reported that, in his prospective study of 3,000 men " * * * the relationship of occupational physical activity to smoking habits revealed that one of six sedentary workers were heavy smokers and one of five strenuous workers were heavy smokers." Weinblatt, in reporting the experience of the Health Insurance Plan of Greater New York (100) also found that a higher proportion (41.9 versus 36.0 percent) of cigarette smokers were classified in the "most active" physical activity category.

The independent and the combined effects between cigarette smoking and physical activity are shown in table 11. The morbidity ratios for myocardial infarctions are derived from published data.

TABLE 11.—Age-adjusted morbidity ratios for myocardial infarctions among smokers and nonsmokers according to physical activity level

Physical activity	Nonsmokers of cigarettes	Cigarette smokers
Most active.....	1.0	2.6
Least active.....	2.4	3.4

SOURCE: Weinblatt, E. (100).

Socioenvironmental Stress

Since 1955, research on socioenvironmental stress in relation to coronary heart disease has increased greatly (83, 92). Among the factors studied that indicate a strong association with coronary heart disease incidence and prevalence is sociocultural mobility, that is, moving from one social setting to another. The interaction of this factor and

cigarette smoking has been reported by Syme (90, 91) in both an urban and rural setting. Apparently in both areas cigarette smokers were more culturally mobile than nonsmokers. The independent effect of cigarette smoking on the incidence of coronary heart disease is shown in the morbidity ratios in table 12 derived from the North Dakota study (91).

TABLE 12.—*Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to sociocultural mobility status*

Sociocultural status	Never smoked cigarettes	Current and former cigarette smokers
Stable.....	1.0	1.5
Highly mobile.....	2.3	3.2

SOURCE: North Dakota study. (91)

Personality Type

Various investigators have long suspected a possible pathogenetic role of the central nervous system in coronary heart disease (35). In a series of reports, Rosenman (81, 82) and Jenkins (51) have described a personality pattern or overt emotional complex which, while associated with other known risk factors, appears to predict coronary heart disease more effectively than do other risk factors. This emotional complex, "which they have termed Behavior Pattern Type A, is composed of an enhanced competitiveness, drive, aggressiveness and hostility, and an excessive sense of time urgency." Recent unpublished data based upon prospective observation of more than 3,000 men for a 4½-year period (51) discloses that smokers have a higher percentage (54 versus 47 percent) of type A persons among them. Moreover, the incidence of coronary heart disease is shown to be related independently to both smoking status and personality type. Morbidity ratios, derived from the incidence data, are shown in table 13 which clearly demonstrates the independent effects of cigarette smoking and its interaction with personality characteristics.

TABLE 13.—*Morbidity ratios of cigarette smokers as compared to nonsmokers by personality type*

Personality type	Nonsmokers of cigarettes	Cigarette smokers
Behavior type B.....	1.0	2.0
Behavior type A.....	2.5	4.4

SOURCE: Unpublished data from Western Collaborative Group Study, San Francisco, Calif. (82).

Multiple-Risk Factors

The method of analysis traditionally employed by epidemiologists, that of the comparison of rates for multiple cross-classifications of the data, generally requires a large study population at relatively high incidence of significant events. Since coronary heart disease incidence rates are low and study populations are necessarily small because of practical and practicable limitations, definitive analysis of the independence and interaction between risk factors have generally been restricted to two factors at a time. Truett (95) applied a multiple logistic function proposed by Cornfield to investigate the independent effect on the incidence of coronary heart disease of seven risk factors: Age, serum cholesterol, systolic blood pressure, relative weight, hemoglobin, cigarettes per day, and ECG abnormalities. The method was used in the analysis of data compiled in the Framingham study during a 12-year period. A discriminant function coefficient was computed for each risk factor. These coefficients represent the relative importance of each factor with respect to the other six factors in the development of coronary heart disease. While theoretical considerations underlying the logistic risk function are not fully satisfied by the actual data, the approximation given by the function to observed rates is very good.

Consequently, Truett and Cornfield believe that the present computations permit the conclusion that "the most important risk factors, aside from age itself, are cholesterol, cigarette smoking, ECG abnormality, and blood pressure" (95).

MANIFESTATION OF CORONARY HEART DISEASE

Coronary heart disease is essentially comprised of three major manifestations or subcategories:

1. Fatal myocardial infarctions, including sudden deaths attributed to coronary heart disease;
2. Nonfatal myocardial infarction; and
3. Angina pectoris.

Generally, investigators in their analysis of the relationship of risk factors to the incidence of coronary heart disease have not subdivided the observed coronary events into the three major subcategories primarily because the paucity of events in each category did not permit definitive conclusions on any differences observed. However, the pooling of data from some of the larger prospective studies holds promise of a more complete analysis of the independent and synergistic effects of each risk factor on each of the subcategories of coronary disease. Findings from these analyses might provide some insights into the underlying pathophysiological mechanisms through which a risk factor operates. The pooled data from the Albany and Framingham studies and data from the HIP study include the observed associations of

cigarette smoking with each of the three major manifestations. Morbidity ratios have been derived from these studies and are presented in table 14.

TABLE 14.—*Age-adjusted morbidity ratios for subcategories of coronary heart disease among smokers and nonsmokers*

Disease category	Framingham-Albany		Health insurance plan	
	Non-smokers of cigarettes	Cigarette smokers	Non-smokers of cigarettes	Cigarette smokers
Fatal myocardial infarction.....	1.0	2.4	1.0	2.1
Non-fatal myocardial infarction.....	1.0	2.3	1.0	1.8
Angina pectoris.....	1.0	1.1	1.0	1.7

SOURCE: Second Report of the Combined Experience from Albany and Framingham Studies (50). Unpublished Data from Health Insurance Plan Study (100).

The association of cigarette smoking to angina pectoris is not a consistent one. A clear-cut association was found in the Health Insurance Plan Study (ratio of 1.7); a similar association is also found in unpublished data from Framingham considered separately. However, no association between cigarette smoking and the incidence of angina pectoris was found in the Albany experience. Cederlof (19), in his analysis of prevalence data on angina pectoris obtained by questionnaire, found no statistically significant difference in prevalence rates between 453 monozygotic twin pairs with dissimilar smoking habits. In a larger study of about 9,000 persons from the twin register where genetic factors were uncontrolled, Cederlof (19, 20) did find a significantly higher prevalence of angina pectoris among smokers than nonsmokers, particularly in men (ratio of 1.6) (67).

Friedman (42) and Epstein (36) have clearly described the inherent biases in prevalence studies which may lead to findings of risk gradients that are different from those obtained in prospective incidence studies. One of these limitations is that fatal cases are under-represented in a prevalence survey. Thus, since it appears that cigarette smoking is more closely related to the incidence of fatal myocardial infarctions than to other forms of coronary heart disease, it is expected that morbidity ratios derived from prevalence surveys would be lower than those computed from incidence data. With these restrictions in mind, Russek (83) in a survey of 12,000 men in 14 occupational groups found that the morbidity ratio of coronary heart disease prevalence among cigarette smokers was as high as 1.8. In contrast, in a study of 77 identical and 89 fraternal twins in Sweden, comparing smokers with their respective nonsmoking twins, Lundman (67) reported no excess prevalence of overt or silent coronary heart disease. However,

the prevalence of these conditions, as Lundman concluded, "was too low to permit of definitive conclusions."

CARDIOVASCULAR RESPONSE TO SMOKING AND/OR NICOTINE

As noted in the Surgeon General's 1964 Report, nicotine has definite physiologic effects on the cardiovascular system of experimental animals and of man. These include increases in heart rate, systemic arterial pressure, cardiac output, stroke volume, and velocity of myocardial contraction, all resulting in an increased myocardial tissue oxygen demand (16). Coronary blood flow studies will be reported in the next section under a separate subheading. These effects parallel those observed with catecholamines (epinephrine and norepinephrine). The effects can be blocked by the injection of tetraethylammonium chloride and markedly reduced by adrenalectomy (22). Nicotine has been repeatedly shown to release endogenous catecholamines (57, 58, 59, 60, 102). However, the mechanism by which nicotine affects the cardiovascular system is more complex than the release of catecholamines from the adrenal medulla. Direct and indirect (via the carotid body and other chemoreceptors) stimulation of the vasomotor center, stimulation of sympathetic ganglia, release of norepinephrine from local stores, and release of antidiuretic hormone are included among other postulated mechanisms of action involved in nicotine's effect on the cardiovascular system (16, 63, 85).

Coronary Blood Flow in Normal Subjects

The action of smoking and/or nicotine on the coronary blood flow of normal human subjects has not yet been definitively established, but apparently normal subjects can increase their coronary blood flows sufficiently to maintain a compensatory blood supply to the myocardium despite the increased myocardial tissue demand for oxygen caused by cigarette smoking. Earlier findings of increased coronary blood flow in normal men, in response to cigarette smoking (11), were not reproduced in a more recent study (16). In this latter study, although a trend towards a slight increase in coronary blood flow was observed in the particular normal persons studied, it was not significant.

Direct injection of nicotine into the left coronary artery of dogs under conditions of constant flow rate resulted in increased coronary vascular resistance (33, 64). This response could be reduced by vagal nerve stimulation or prior administration of acetylcholine; an immediate increase in cardiac contractile force was also observed that could be similarly reduced. It was concluded that these responses to nicotine resulted from sympathetic nervous system activity or from the release of catecholamines by myocardial chromaffin tissue (64).

Blood from the smoke-exposed lung tissue of dogs, directly perfused

into the coronary artery, failed to increase coronary resistance (38). This effect was thought to be secondary to that of histamine, known to act as a coronary vasodilator, which apparently is released from the lung tissue of dogs during their exposure to smoke (8).

When blood from the smoke-exposed lung was perfused through the systemic circulation of dogs while the coronaries were being perfused with non-smoke-exposed blood, the typical release of catecholamines occurred with many of the usual effects on cardiovascular parameters except that the coronary vascular resistance increased under these experimental conditions, apparently due to the increased activity of the sympathetic nervous system (38).

Since it is well known that exposing dogs to cigarette smoke without isolating and separately perfusing the coronary circulation normally results in an increase of the coronary blood flow (38), the manipulation of experimental conditions as described suggests that there is a masking effect by the catecholamines on nicotine's direct action on the coronary circulation (38).

These studies may relate, by analogy, to humans and indicate that smoking, in "normal" individuals, may produce at least two actions that can affect coronary blood flow: (1) a decrease in coronary blood flow by a possible direct action of nicotine on the coronary circulation (demonstrated in dogs), and (2) an increase in coronary blood flow as the usual resultant of varying responses to the intermediating action of catecholamines and other physiologic processes (demonstrated in both animals and humans).

Coronary Blood Flow in Subjects with Coronary Heart Disease

The effect of cigarette smoking on coronary blood flow was studied in patients with coronary heart disease (79). As was seen in normal subjects, significant increases in heart rate, arterial pressure, and cardiac output were noted. In contrast to the normal individuals studied, patients with coronary heart disease distinctly showed a much less significant compensatory increase in their coronary blood flows. These results were confirmed by a later study (16), using the Rubidium 84 method to estimate coronary blood flow. This study also showed that in the coronary patients studied, there was no adequate compensatory increase in coronary blood flow to meet the increased myocardial tissue demand for oxygen. Coronary blood flow apparently decreased as a result of cigarette smoking, in this particular study group of coronary patients. Although the decreases noted were not marked, they were statistically significant, and indicated that a difference existed between these coronary patients as compared to the normal subjects studied.

A difference in the coronary blood flow response to nitroglycerine has also been demonstrated in normal subjects compared to subjects with coronary heart disease. This was shown in studies using the

nitrous oxide (18, 44) and the Rubidium 84 (15) methods to measure coronary blood flow. In response to nitroglycerine the normal individuals generally increased their coronary blood flow significantly, but the coronary patients generally did not.

Animal studies have also demonstrated the decreased ability of atherosclerotic coronary arteries to increase coronary blood flow, as compared to the coronary arteries in normal animals (94). Dogs with experimentally produced coronary artery insufficiency also show this decreased ability (12). Similar differences between animals with normal coronary arteries as compared to atherosclerotic coronary arteries have been demonstrated in response to ergonovine (80).

The above studies indicate that the effect of nicotine upon the cardiovascular system, mediated in part by the action of released catecholamines, is generally to increase heart rate and cardiac output, and to raise systemic arterial pressure temporarily. Findings concerning the effect of nicotine on coronary blood flow are presently thought to be largely due to the indirect effects of nicotine upon the cardiovascular system. Other animal studies indicate that there may be a direct action of nicotine on the coronary vasculature to increase coronary vascular resistance, thus tending to reduce coronary blood flow. There are no human studies on the direct action of nicotine by itself on the coronary vasculature; such studies, involving the direct injection of nicotine into diseased human coronary arteries, might be dangerous. Normal individuals apparently can increase their coronary blood flows to compensate for the increased myocardial tissue oxygen demand, but apparently some patients with coronary heart disease cannot, as shown by their response to smoking.

Thus some patients with coronary heart disease may be at a particular disadvantage when smoking and under other stresses since their coronary arteries apparently cannot dilate to supply blood flow adequate to meet the increased oxygen demand associated with nicotine-induced catecholamine release. The interaction of the above effect with recent findings concerning carbon monoxide, described in the next section, may be especially important in those individuals with coronary heart disease. The present studies indicate that the effect of cigarette smoking on coronary blood flow, in the presence of pre-existing coronary heart disease, may, in part, contribute to the increased incidence of acute myocardial infarctions that have been observed to be associated with cigarette smoking. No relationship between the smoking effect on coronary blood flow and the pathogenesis of coronary atherosclerosis per se is presently suggested. Additional research is needed.

Carbon Monoxide Effect

The gaseous phase of cigarette smoke contains about 4 percent carbon monoxide. This quantity can increase the levels of carboxyhem-

globin saturation of cigarette smokers from 2 percent to 10 percent (21). The average nonsmoker, depending on environmental exposure, usually has less than 2 percent carboxyhemoglobin saturation (10). Since smokers of one pack or more a day may have chronically elevated carboxyhemoglobin levels of more than 4 percent (9), there may be appreciable differences in the carboxyhemoglobin levels between some heavy cigarette smokers and nonsmokers.

In addition to displacing oxyhemoglobin, carbon monoxide effects a shift in the oxygen-hemoglobin dissociation curve (2, 3, 4 5, 6). This may result in a decreased release of oxygen at the tissue level. A series of studies (61, 62) has been performed on young adults to analyze the effect of cigarette smoking on carboxyhemoglobin levels, and the consequent effect on some parameters of cardiopulmonary function. An increased post exercise oxygen debt was observed after cigarette smoking as compared to controls. This, in part, may reflect not only ventilatory disturbances but also a decreased supply of oxygen in the blood due to the carbon monoxide effect, resulting in less available oxygen to meet the increased tissue demand. Similar post-exercise oxygen debts have been noted after inhalation of enough carbon monoxide to produce comparable blood levels of carboxyhemoglobin (21).

The consequence of the smoking/carbon monoxide effect appears to be especially important in the myocardium where relatively more oxygen is normally extracted from the coronary circulation as compared to other organ systems. (Coronary venous blood usually has an oxygen saturation of less than 25 percent, whereas blood leaving some other organs is about 75 percent saturated with oxygen (45).)

Dogs were exposed to carbon monoxide to elevate their carboxyhemoglobin saturation levels (9). In response to inhalation of carbon monoxide there was an increase in coronary blood flow but a decrease in coronary arterial-venous oxygen differences. Patients with coronary heart disease were also studied following inhalation of enough carbon monoxide to elevate their carboxyhemoglobin saturation levels to the range of 5 to 12 percent (9). In response to carbon monoxide there was generally an increase in the cardiac output and the coronary blood flow in most of the patients. While the systemic arterial-venous oxygen differences varied, either increasing or decreasing, the coronary arterial-venous oxygen differences decreased, indicating a decreased oxygen extraction by the myocardial tissue despite the myocardium's increased demand for oxygen. These decreases in myocardial oxygen extraction are related to increases in the carboxyhemoglobin saturation levels. It was observed that some patients evidently could compensate by increasing their coronary blood flows adequately to supply the myocardial tissue with sufficient oxygen, as indicated by a rise in myocardial oxygen uptake in these individuals. However, the other

patients with coronary heart disease, evidently more severe, could not increase their coronary blood flow rate enough to compensate for the decreased oxygen carried by the blood. This latter group of patients, even though they had increased cardiac output, had less significant increases of coronary blood flow than those noted in the first group of patients. The coronary arterial-venous oxygen differences and the myocardial tissue oxygen uptakes both decreased, indicating that the myocardial tissue oxygen demand was not being met entirely.

The reduction in the amount of oxygen available to the myocardial tissue caused by the absorption of carbon monoxide from tobacco smoke may be especially critical in persons with pre-existing coronary heart disease, especially when they cannot significantly increase coronary blood flow to compensate for increased myocardial tissue oxygen demand. The carbon monoxide effect may, in part, contribute to the increased incidence of myocardial infarctions that occur in cigarette smokers. Additional research is needed.

Studies on In Vitro Thrombus Formation

Recent studies have indicated that cigarette smoking may accelerate thrombus formation of human blood *in vitro*. Platelet adhesiveness, as measured by *in vitro* tests, also appears to be increased by cigarette smoking (1, 43, 71, 87). Other studies, comparing smokers with non-smokers, indicate that the platelet survival time of the smokers is shortened (73) and the platelet turnover rate is increased (72). Studies of animals show there is also an increased tendency for the platelets to adhere to the vascular endothelium.

Platelet adhesiveness is reported to be increased in *in vitro* studies using the Chandler rotating loop (32, 33, 34); these studies generally show a consistent acceleration of the rate of thrombus formation. Other *in vitro* tests show changes in thrombus formation and some parameters of coagulation as a result of smoking (56, 66, 87). However, problems in experimental design and the multiplicity of tests used, measuring either the same or overlapping portions of the complicated coagulation process with varying results, cause difficulty in evaluating these results (71).

The mechanism of changes in characteristics of the platelets in smokers is being investigated, but there are indications that the release of catecholamines, especially epinephrine, caused by the absorption of nicotine during smoking may be intimately involved (71, 72). In small doses, epinephrine has been shown to promote thrombus formation and coagulation, but in large doses it inhibits these processes. Changes in the electrical charge of the platelet membrane have also been implicated in increasing platelet adhesiveness (101), increasing adherence to the vascular endothelium, and accelerating thrombus formation as measured by the Chandler loop method. Some of the alterations in thrombus formation may be mediated by an interaction

with serum-free fatty acids and cholesterol (70) but current evidence suggests that inhalation of cigarette smoke acts primarily through other independent factors (101). Thus, cigarette smoking may cause an acceleration of the *in vitro* thrombus formation of human blood. It is reasonable to suspect that cigarette smoking, in part by affecting the thrombus-forming process in human blood, may account for some of the excess coronary heart disease deaths that occur in cigarette smokers, especially some of the deaths certified as "acute coronary thrombosis." Further research is necessary before any definite conclusion can be made.

AUTOPSY STUDIES

The two most significant pathological studies of the relationship of smoking history to atherosclerotic changes in human coronary arteries have been reported by Auerbach and Strong. Auerbach (7) studied 1,372 males for whom a smoking history was available and who had died of causes other than coronary heart disease. He found that the percentage of men with an advanced degree of coronary atherosclerosis was higher among cigarette smokers than among nonsmokers, and that the percentage increased with amount of cigarette smoking. Both among smokers and nonsmokers the percentage of men with advanced coronary atherosclerosis also increased with age. This relationship held up even when the following were excluded: men with a history of diabetes, men who had died of any type of heart disease, and men whose hearts weighed 400 gm. or more. A matched set analysis was also carried out (reincluding some diabetics and heart disease deaths) and again the percentage of men with advanced coronary atherosclerosis was less among nonsmokers than among men who had been current cigarette smokers, and this percentage increased with the amount smoked.

Strong (39) in a study of coronary arteries from 645 autopsied males, 20 to 64 years of age, excluded patients with diseases he thought to be associated with smoking (emphysema, lung cancer, etc.), or with coronary heart disease (myocardial infarction, hypertension, diabetes, stroke, etc.). He found that the mean percent of coronary intimal surface occupied by raised atherosclerotic lesions was approximately twice as great in heavy smokers (25+ cigarettes/day), and about one-third greater in light smokers (less than 25/day), than in nonsmokers. Calcified lesions and mean coronary wall thickness measured radiographically were on the average highest in heavy smokers and lowest in nonsmokers. Differences among these smoking categories were generally greatest at younger ages.

These autopsy studies suggest that smoking, in addition to the acute immediate effect associated with the act of smoking, has a chronic effect leading to advanced degrees of atherogenesis. However, these findings may, in part, reflect the differences noted between

smokers (7, 89), particularly heavy smokers, and nonsmokers in regard to greater obesity, higher dietary fat intake, and higher serum cholesterol levels. Further analyses of autopsy series are needed to determine the independent effects of cigarette smoking on atherogenesis.

SMOKING AND CEREBROVASCULAR DISEASE

An increasing amount of evidence has accumulated in the past few years relating the development of clinical cerebrovascular disease to cigarette smoking. Most of this information has come from the prospective mortality studies.

Hammond has reported the following data from his large prospective study (47), noted in table 15.

TABLE 15.—*Cerebral vascular lesions. Age-standardized death rates, by type of smoking (lifetime history) and age at start of study*

	Age			
	45-54	55-64	65-74	75-84
CVL death rates per 100,000 person-years				
MEN				
Never smoked regularly	28	92	349	1,358
Pipe, cigar	25	100	369	1,371
Cigarette and other	28	129	361	990
Cigarette only	42	130	477	1,168
Total	35	116	391	1,272
WOMEN				
Never smoked regularly	18	57	228	1,082
Cigarette	38	88	315	1,277
Total	25	64	238	1,091
CVL mortality ratios				
MEN				
Never smoked regularly	1.00	1.00	1.00	1.00
Pipe, cigar89	1.09	1.06	1.01
Cigarette and other	1.00	1.40	1.03	.73
Cigarette only	1.50	1.41	1.37	.86
WOMEN				
Never smoked regularly	1.00	1.00	1.00	1.00
Cigarette	2.11	1.54	1.38	1.18

SOURCE: E. C. Hammond (47).

Between the ages of 45 and 74 the death rates from stroke for male smokers were 37 to 50 percent higher than those for male nonsmokers of comparable age. In female smokers the death rates from stroke were 38 to 111 percent greater than those for nonsmokers. Above the age of 74 the differences between the two groups were much less.

The data in Table 16 concerning smoking and death rates from stroke are derived from the U.S. veterans study (52).

TABLE 16.—*Mortality ratios and death rates for stroke as underlying cause among current smokers of cigarettes only*

	Quantity of cigarettes smoked per day				
	0	1-9	10-20	21-39	40+
Mortality ratio (all ages).....	1. 00	1. 51	1. 42	1. 70	1. 59
Death rates:					
Age 55 to 64.....	59	92	112	125	130
Age 65 to 74.....	280	323	312	382	502

SOURCE: U.S. veterans study (52).

When stroke was certified as the principal cause of death, the death rates for smokers were higher than for nonsmokers; however, no pronounced increase was noted in the mortality ratios as the degree of smoking increased. The death rates from stroke for all ages was 59 percent higher in heavy smokers (40 or more cigarettes) than in nonsmokers.

TABLE 17.—*Mortality ratios and death rates for stroke as the underlying or contributory diagnosis among current smokers of cigarettes only*

	Quantity of cigarettes smoked per day				
	0	1-9	10-20	21-39	40+
Mortality ratio (all ages).....	1. 00	1. 45	1. 45	1. 75	1. 83
Death rates:					
Age 55 to 64.....	101	152	174	195	2 6
Age 65 to 74.....	424	514	520	616	724

SOURCE: U.S. veterans study (52).

Stroke, listed as either the underlying or contributory cause of death on the death certificate, was also associated with progressively increasing mortality ratios and death rates as the extent of smoking increased. Heavy smokers here had an 83 percent greater mortality from stroke than nonsmokers.

Mortality data by underlying cause of death may often be misleading, particularly when stroke is concerned. Many stroke patients have

concomitant coronary heart disease, or may develop pneumonia and other complications that may hasten death. The death certificate may carry stroke as the underlying cause or as the contributory cause of death, depending upon the interpretation of the physician at the time. The important addition of these data is that smoking is associated with a higher mortality from stroke, whether the stroke is recorded as either the underlying cause or as the contributory cause of death.

These two studies indicate that smoking may be associated with a higher mortality from stroke in the relatively younger age groups (under age 74). More than one-half the strokes that occur each year are in the group above age 75 and in this group there is no evidence relating smoking to cerebrovascular disease.

Another large study has been conducted analyzing the mortality of 50,000 former students who entered Harvard University or the University of Pennsylvania during the years 1916-50 (74, 75, 76). From this population 171 deaths from cerebrovascular accidents have been identified. A review of the medical records from their college years has been carried out, and selected factors were correlated with the later occurrence of stroke. Seven precursive "risk factors" present at the time of college attendance have been defined: Cigarette smoking, high blood pressure, excess body weight, short stature, a history of early parental death, a history of nonparticipation in college sports, and a history of "heart consciousness" (also shown to be correlated with coronary heart disease). Cigarette smoking and a history of early parental death were more strongly correlated with thrombotic stroke than with hemorrhagic stroke. Students who smoked more than 10 cigarettes daily were at twice the risk of having a fatal stroke than were those who smoked less or not at all.

In 1965 the Framingham study (54) reported that while an excess development of thrombotic brain infarction appeared to be associated with cigarette smoking, statistically significant differences could not be demonstrated with the small number of cases available at that time. More recent data from Framingham indicates that cigarette smoking increases the risk of stroke in males. The relatively small number of women smokers had too few strokes for adequate analysis.

The new epidemiological evidence, then, indicates that cigarette smoking may be more closely associated with cerebrovascular disease in the population between the ages of 45 and 74 years than was previously indicated. If cerebrovascular thrombosis (thrombotic brain infarction) accounts for this association, it is possible that some of the considerations of how cigarette smoking may produce coronary thrombosis also apply to the pathogenesis of cerebrovascular disease. Further research is essential to understand the relationships that exist between cigarette smoking and cerebrovascular disease.

SMOKING AND AORTIC ANEURYSM

Additional information on mortality data concerning aortic aneurysm has been provided by the U.S. veterans study (52) and the Hammond (47) studies, as noted in tables 18 and 19, respectively.

TABLE 18.—*Mortality ratios and age-standardized death rates for aortic aneurysm in U.S. veterans, current smokers of cigarettes only*

	Number of cigarettes smoked per day				
	0	1-9	10-20	21-39	40+
Mortality ratio.....	1. 00	2. 12	5. 53	5. 95	7. 26
DEATH RATES					
Age:					
55 to 64.....	6	13	27	43	44
65 to 74.....	25	57	123	157	221

SOURCE: U.S. veterans study (52).

TABLE 19.—*Mortality ratios and age-standardized death rates for aortic aneurysm*

	Age 45-64 years		Age 65-79 years	
	Females	Males	Females	Males
Mortality ratio.....	3. 89	2. 62	3. 33	4. 92
Death rates.....	¹ 4(1)	18(7)	43(13)	118(24)

¹ Numbers in parentheses indicate death rates of those who never smoked regularly.

SOURCE: Hammond, E. C. (47).

It is apparent that there is a close association between cigarette smoking and death caused by aortic aneurysms.

Thus, the additional evidence confirms the previously observed association between cigarette smoking and death due to nonsyphilitic aortic aneurysm.

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CHAPTER 2

Smoking and Chronic Bronchopulmonary Diseases (Non-neoplastic)

CONTENTS

	<i>Page</i>
Introduction.....	89
Chronic Bronchopulmonary Disease Mortality.....	90
Chronic Bronchopulmonary Disease Morbidity.....	96
Studies Relating Smoking to Respiratory Symptoms.....	96
Studies Relating Smoking to Pulmonary Function.....	99
Relation of Smoking to Heredity or to Constitutional Factors ..	101
Pathology Studies.....	104
Animal Experiments.....	106
Ciliotoxic Effects of Cigarette Smoke.....	107
Other Factors Associated with Chronic Bronchitis or Em- physema or Both.....	108
Additional Considerations Regarding Smoking and Em- physema.....	110
Cited References.....	111
Supplemental References.....	117

INTRODUCTION

PURPOSE OF THIS REPORT

This report reviews additional pertinent data relative to smoking and chronic bronchopulmonary diseases—specifically chronic bronchitis and pulmonary emphysema.

The reader is referred to the Surgeon General's 1964 Report (68) and recent textbooks for background information on the chemistry of tobacco smoke, the metabolism and toxicity of specific components of tobacco smoke, the physics of its retention in the air passages and the lungs, and the mechanics of pulmonary function.

DEFINITIONS

The scope of this chapter will be limited to emphysema and chronic bronchitis and it may be useful to present definitions of both terms. There have been many definitions of chronic bronchitis and emphysema. Those used in the Surgeon General's 1964 Report had been proposed by the American Thoracic Society in 1962 (37). With the increasing public health interest in chronic bronchopulmonary disease, attempts have been made to develop precise definitions to categorize these diseases and to isolate them satisfactorily from other pulmonary conditions. A task force sponsored by the Chronic Respiratory Diseases Control Program of the Public Health Service and the National Tuberculosis Association deliberated this together with related problems for a week in October 1966. They adopted the following definitions (71):

Chronic bronchitis is a clinical disorder characterized by excessive mucous secretion in the bronchial tree. It is manifested by chronic or recurrent productive cough. The diagnosis of chronic bronchitis can be made only if other bronchopulmonary or cardiac disorders are excluded as the cause for these symptoms. The predominant pathologic change is hypertrophy and hyperplasia of the mucous secreting glands in the trachea and bronchi.

Pulmonary emphysema is an anatomic alteration of the lung characterized by destruction of alveolar walls accompanied by abnormal enlargement of the air spaces distal to the terminal, nonrespiratory bronchiole."

These definitions will be used to describe chronic bronchitis and emphysema as understood in the present report. They are being used

to emphasize the lack of progress in defining the two conditions for purposes of differentiating them from other diseases of the lung. Reference may be made to the Surgeon General's 1964 Report where nearly identical definitions will be found.

Inability to distinguish between chronic bronchitis and emphysema has hampered medical research and exchange of information. The P.H.S.-N.T.A. task force report states further:

"Although patients having only chronic bronchitis tend to have more cough and sputum than do those having only pulmonary emphysema, the array of symptoms, physical findings, and pulmonary physiologic abnormalities are similar in both diseases.

"Chronic bronchitis and emphysema coexist in many patients * * *"

This statement may help to explain some of the difficulties encountered by research workers in studying these diseases and why the researchers are limited to describing symptoms and signs observed in the populations under investigation. It may also explain why it is difficult to distinguish these conditions in the present report which seeks to record the research findings related to smoking and chronic respiratory disease published since the Surgeon General's 1964 Report. Research findings on both diseases are not considered separately in this report but are grouped in population studies, pathology studies, and animal experiments. Additional considerations pertinent to pulmonary emphysema are then provided.

CHRONIC BRONCHOPULMONARY DISEASE MORTALITY ¹

Mortality from chronic bronchopulmonary diseases has continued the upward trend well established at the time of publication of the conclusions cited in the Surgeon General's 1964 Report. Deaths in the United States from emphysema or chronic bronchitis or both have risen steadily from about 3,000 in 1950 to more than 20,000 in 1964, as can be seen in table 1.

TABLE 1.—*Mortality from emphysema and/or chronic bronchitis (ISC codes 501, 502, 527.1)*

Year	Number of deaths	Year	Number of deaths	Year	Number of deaths
1964.....	20, 208	1959.....	10, 433	1954.....	4, 877
1963.....	19, 443	1958.....	9, 328	1953.....	4, 657
1962.....	15, 915	1957.....	8, 136	1952.....	3, 846
1961.....	13, 302	1956.....	6, 535	1951.....	3, 660
1960.....	12, 426	1955.....	5, 616	1950.....	3, 157

SOURCE: Vital Statistics of the United States, 1950-1964 (70).

¹ All death rates throughout this chapter are per 100,000 population, unless otherwise indicated.

The increase and aging of the population during the same period does not account for this rise. Age-adjusted mortality rates for emphysema without mention of chronic bronchitis increased about ten times for men, from 1.3 per 100,000 in 1950 to 12.6 in 1964. A similar, although perhaps somewhat less dramatic, increase occurred among women, from 0.2 per 100,000 in 1950 to 1.6 in 1964. Death rates from chronic bronchitis rose less precipitously, doubling during the same period (69, 70). How much of this increase is the result of improved diagnosis of these diseases and how much the result of a true change in mortality patterns cannot be determined at the present time. Associations have been demonstrated between these conditions and smoking.

POPULATION STUDIES

Included in this broad category are investigations that collected information from a group or groups of persons either by a series of questions, by some form of physical examination, or by a review of recorded data such as hospital records and death certificates.

PROSPECTIVE STUDIES

In the Surgeon General's 1964 Report, findings from seven prospective studies were presented. Additional data have been reported from four of these investigations in the past 3 years. Information relevant to smoking and chronic respiratory disease will be summarized here.

The study of mortality among policyholders of U.S. Government Life Insurance policies available to persons who served in the Armed Forces between 1917 and 1940 was initiated in 1952. Almost all the 293,658 policyholders were white males. Recently Kahn (44) published a report that included all deaths from July 1954 through December 1962, a period of 8½ years.

The relation of cigarette smoking to death from bronchitis and emphysema is presented by mortality ratios in table 2 and by specific risk of mortality in table 2A. Given the definitions previously cited, these tables also illustrate the difficulties in separating these diseases. The first row of table 2 gives combined mortality ratios and the next two rows give the same data in an attempt to delineate the specific diseases. Mortality ratios are given by the number of cigarettes smoked per day at the time the men were enrolled in the study. Mortality from these diseases is much higher among cigarette smokers than among those who never smoked and rises with the number of cigarettes smoked daily. The ratios are much higher for emphysema alone than for chronic bronchitis with or without mention of emphysema.

A similar study of veterans was begun in Canada in 1955. Answered questionnaires were returned by nearly 78,000 men whose subsequent mortality for a period of 6 years was recently analyzed by Best and

his associates (12). Deaths from chronic bronchitis and emphysema have been summarized in table 3 which gives mortality ratios by the number of cigarettes smoked each day. Here, again, the mortality is much higher among smokers and is directly related to the number of cigarettes smoked. The mortality ratios reported for both diseases combined are similar to those reported for the U.S. Veterans study.

TABLE 2.—Age-adjusted mortality ratios for current smokers of cigarettes only, by number of cigarettes smoked daily

Cause of death	Cigarettes smoked per day at entrance to study				
	Occasional or never smoked	1-9	10-20	21-30	40+
Bronchitis or emphysema or both (500-502, 527.1).....	1.0	4.6	10.0	11.8	18.2
Bronchitis with or without emphysema (500-502).....	1.0	3.6	4.5	4.6	8.3
Emphysema (527.1).....	1.0	5.3	14.0	17.0	25.3

SOURCE: U.S. Veterans study (44).

TABLE 2A.—Age-specific annual probabilities of death per 100,000¹ person-years, for current smokers of cigarettes only

	Cigarettes smoked per day at entrance to study					All quantities
	Occasional or never smoked	1-9	10-20	21-30	40+	
Chronic bronchitis and/or emphysema:						
Age 55 to 64.....	2	12	32	30	39	29
Age 65 to 74.....	10	66	100	141	322	113
Chronic bronchitis:						
Age 55 to 64.....	1	5	5	5	5	4
Age 65 to 74.....	5	15	22	30	46	23
Emphysema without bronchitis:						
Age 55 to 64.....	1	7	27	26	34	25
Age 65 to 74.....	5	52	78	111	276	90

¹ Annual probabilities of death at each single year of age were combined into 10-year age groups by using weights proportional to the distribution of the U.S. male population in 1960. Not shown if less than 50 person-years of observation at any single year of age in the 10-year interval.

SOURCE: U.S. Veterans study (44).

When the two diseases are separated, the ratios for emphysema in the Canadian study are similar to those for chronic bronchitis in the U.S. study, and the ratios for chronic bronchitis are similar to those attributed to emphysema in the United States. This illustrates the

problems of definition and one of the difficulties of direct comparison between studies, especially when different countries are involved.

TABLE 3.—*Age-adjusted mortality ratios for smokers of cigarettes only by number of cigarettes smoked daily*

Cause of death	Cigarettes smoked per day at entrance to study			
	Non-smokers	1-9	10-20	21+
Bronchitis or emphysema or both.....	1.0	6.1 ¹	10.0 ¹	10.4 ¹
Bronchitis with or without emphysema (500-502).....	1.0	7.0	13.7	14.6
Emphysema (527.1).....	1.0	4.8	6.1	6.9

¹ Calculated from (18).

SOURCE: Canadian Pensioners study (18).

A study among British physicians, the first of the large prospective studies, was started in 1951 with the sending of a short questionnaire to the 59,600 registered physicians then resident in the United Kingdom. Usable replies were received from 34,455 men and 6,192 women. Ten years of observation of mortality in relation to smoking was recently reported for this population by Doll and Hill (29, 30). Their findings on mortality from chronic bronchitis as related to smoking included emphysema and are given in table 4. Only the standardized death rates were presented in the report but the mortality ratios have been calculated from them to offer an easier comparison with the other two studies. Again, it is clear that mortality from these combined diseases (no attempt was made to differentiate them in the published report) is strongly and directly related to the amount of cigarette smoking.

TABLE 4.—*Standardized death rates, per 100,000 population, for bronchitis and emphysema for male smokers of cigarettes only, by number of cigarettes smoked daily*

Cause of death	Cigarettes smoked per day at entrance to study			
	Never smoked	1-14	15-24	25+
Bronchitis (including emphysema—502, 527.1).....	5	34	64	106
Mortality ratios.....	1.0	6.8	12.8	21.2

SOURCE: Study of British Physicians (29, 30).

The fourth of the prospective studies is the largest. More than 1 million men and women living in 25 States were enrolled in this investigation in late 1959 and early 1960. A report of the first 4 years of observation was published recently by Hammond (36) and mortality from emphysema and chronic bronchitis as related to smoking is given in table 5. A slight departure from the usual assignment of cause of death should be mentioned. When the cause of death was listed as chronic bronchitis with emphysema, it was combined with emphysema alone. For this reason, the cause of death in table 5 is not quite the same as any of the causes listed in the other tables. Again, it is clear that mortality from these entities is related to smoking for both men and women. This was the only one of the four studies with enough women enrolled to provide meaningful data.

TABLE 5.—Mortality ratios for deaths due to emphysema and bronchitis with emphysema for cigarette smokers—men and women in 2 age groups†

Cause of death	Men (age in years)		Women (age in years)	
	45-64	65-79	45-64	65-79
Emphysema and bronchitis with emphysema (502, 527.1)-----	6.5	11.4	4.9	7.5 ¹

† Mortality ratios of nonsmokers in the above categories are 1.00 by definition.

¹ Calculated from (36).

SOURCE: Hammond, E. C. (36).

Before summarizing the data presented from these four investigations, two further points should be made. Excessive mortality was largely confined to cigarette smokers. The mortality ratio for chronic bronchitis and emphysema, for pipe and cigar smokers combined, in the U.S. veterans study, was only 0.99; in the Canadian study it was about 1.6 (based on only nine deaths); in the study of men from 25 States it was 1.37; and among British doctors the standardized death rate was 15 (compared with five among nonsmokers). Whatever may be the relationship of pipe and cigar smoking to chronic bronchitis and emphysema, it is clear that it is substantially less important than the relationship of cigarette smoking.

In two of these studies, stopping cigarette smoking is seen to have an effect on subsequent mortality from chronic bronchitis and emphysema. In the course of the followup of the British physicians (29, 30) it was possible to estimate the number of years a man continued smoking after he had answered the initial questionnaire. For chronic bronchitis the mortality rates at first increased after cessation of smoking and later fell well below the rate for men who continued to smoke. The death rate from chronic bronchitis, per 100,000

ex-smokers of 5 years or more was 37 compared with a rate of 59 for all other smokers. Similarly, in the study of U.S. veterans, the mortality ratio for chronic bronchitis and emphysema was 10.1 for all male current cigarette smokers but only 7.6 for men who had stopped smoking for reasons other than "Doctor's orders."

RETROSPECTIVE STUDIES

Wicken (75) made a study of lung cancer and bronchitis mortality in Northern Ireland. During the 3 years, 1960-62, a total of 1,262 men and 630 women, aged 35 years or more, were certified as having died of bronchitis. For each of these persons a control was selected—the next person in the Register of the same sex and 5-year age group who last resided in the same area and who died of a nonrespiratory illness. Personal interviews with relatives of the decedents were carried out for about 94 percent of the subjects and controls to determine the decedents' smoking habits. In addition, a random sample of about 1,500 households in Northern Ireland was selected and one member of each household was interviewed to obtain details of the age, sex, smoking habits, and other information on all adult members. This information on all adult members was used to define the adult population of Northern Ireland in order to calculate death rates.

Bronchitis mortality for both men and women was associated with smoking and directly related to the number of cigarettes smoked daily, as seen in table 6.

TABLE 6.—*Age-standardized death rates per 100,000 population from bronchitis for adults 35 years old and over as related to smoking habits*

	Nonsmoker	Number of cigarettes smoked daily			Smoker of—	
		1-10	11-22	23+	Cigarettes, pipes or cigars	Pipes or cigars
Men	(124) ¹ 64	(245) 189	(300) 220	(168) 284	(62) 99	(289) 118
Women . .	(490) 58	(57) 77	(20) 118	(15) 201	-----	(2) 165

¹ Figures in parentheses show the number of deaths upon which the rates are based.

SOURCE: Wicken study (75).

Using these data, Wicken applied the bronchitis death rates observed among male non-smokers to all the male population of Northern Ireland and estimated that had these rates prevailed, only 45 percent of the male deaths from bronchitis would have occurred.

RÉSUMÉ

Recent data from the four prospective studies and the one retrospective study all reveal, for men, an association between cigarette smok-

ing and mortality from bronchitis and emphysema. All report an increasing gradient of mortality with an increasing amount smoked. This was also true among women although only one prospective study and the retrospective study included enough women to permit calculation of death rates. Mortality was consistently higher among cigarette smokers than among men who smoked pipes or cigars. These are consistent associations that might be expected if there were a causal relation between cigarette smoking and these diseases. In addition, if such a relationship exists, cessation of smoking should be followed by a reduction in mortality. This did occur in the two studies that included information on changes in smoking habits.

These data, then, strongly support the conclusion that cigarette smoking is at least one of the causes of chronic bronchitis and emphysema.

CHRONIC BRONCHOPULMONARY DISEASE MORBIDITY

STUDIES RELATING SMOKING TO RESPIRATORY SYMPTOMS

Most surveys of chronic respiratory disease are confined to the frequency of signs or symptoms of disease. The National Center for Health Statistics, however, in interviews from July 1964 to June 1965, asked about certain chronic conditions including chronic bronchitis and emphysema (72). This was asked in a national sample of 42,000 households containing about 134,000 persons. After answering questions about health for himself and other members of the household, the respondent was asked questions about their smoking habits. A strong relationship was found between smoking habits and the presence of chronic bronchitis or emphysema or both. This is presented in table 7.

TABLE 7.—*Age-adjusted prevalence rates of chronic bronchitis and/or emphysema per 100 persons 17 years and over, by sex, and smoking status—number of cigarettes per day (heaviest amount)*

	Never smoked	Former smokers	Present smokers		
			1-10	11-20	21+
Men.....	1.0	2.5	1.1	2.3	3.3
Women.....	1.2	2.6	1.6	4.0	6.5

SOURCE: National Center for Health Statistics (72, Fig. 5).

In another study of the epidemiology of persistent cough, Wynder (80) and his associates evaluated the smoking habits, occupation, and residence (urban or rural) in a male population comprised of 315 hospital patients in New York, and 315 in California, and of 239 Seventh-Day Adventists living in California who were not hospital patients. Persistent cough was reported from 23 percent of the Adventists (who do not smoke), 45 percent of the New York patients, and 53 percent of the California patients. Coughing was more frequently reported by cigarette smokers than by those who smoked pipes or cigars, as shown in table 8. Inhalers also had a higher rate of persistent cough and the rate of cough increased with smoking in each age group. Wynder found no correlation between urban or rural residence and persistent cough. Analysis of the California group showed a higher rate of persistent cough that was independent of the number of cigarettes smoked.

TABLE 8.—Percent of men with persistent cough as related to smoking habits

	Non-smoker	Pipes/cigars	Cigarettes only			Mixed smoker
			1-10	11-20	20+	
New York patients.....	14	33	45	46	67	51
California patients.....	22	30	45	74	74	66
Seventh-Day Adventists.....	23	-----	-----	-----	-----	-----

SOURCE: Wynder, E. L. et al. (80).

Deane and her associates (28) studied symptoms in relation to smoking in a group of about 500 outside telephone workers over age 40 working in the San Francisco and Los Angeles areas. Symptoms were reported on a modified version of the British Medical Research Council questionnaire. Regardless of the definition of the respiratory symptom—persistent cough and phlegm, persistent cough, phlegm, and shortness of breath—it was consistently experienced by a greater proportion of those who currently smoked cigarettes than those who did not.

Coates and his coworkers (20) also found among 1,584 postal workers aged 40 or more (all employees of the Detroit Main Post Office), that for every symptom—cough and phlegm, chronic phlegm alone, wheezing, shortness of breath—the prevalence was two to three times greater among moderate (15-24 cigarettes per day) and heavy (25 or more) smokers than among those who did not smoke. These differences in symptom prevalence were observed for both men and women but "chronic bronchitis" was reported more often by men, which Coates ascribes to their being heavier smokers. The prevalence of chronic

cough and phlegm among ex-smokers was no greater than in nonsmokers.

Very few studies have been carried out to estimate the association of morbidity and smoking in young people. Peters and Ferris (60) retrospectively tallied the number of visits to the clinic at the University of Health Services for 1,623 Harvard students and 404 Radcliffe students. Smoking information had been gathered on these students in their freshman and senior years. Smokers made significantly more visits to the clinic in total and for respiratory diseases in particular. There was a positive correlation between years smoked and the number of respiratory disease visits.

In contrast to most studies which select population groups, Huhti (43) studied virtually the entire population, age 40-64, in a commune in western Finland. Although it was a mostly rural population, some industrial workers were included. More than 95 percent of the men and women invited responded to the survey. Questionnaires (based on that of the British Medical Research Council) and medical examinations were completed for 730 men and 890 women. Only 18.7 percent of the men were nonsmokers and 21.6 percent ex-smokers, compared with 86.1 percent nonsmokers and 3.6 percent ex-smokers among women. Prevalence of both cough and phlegm production was significantly higher among smokers than nonsmokers as seen in table 9.

TABLE 9.—Percent of men and women with cough (3 months in the year) and with phlegm (3 months in the year), related to smoking habits

	Cigarettes smoked per day			Non-smokers	Ex-smokers
	1-14	15-24	25+		
Cough:					
Men.....	31.5	40.8	42.4	4.1	8.5
Women.....	10.4	(3 of 7 women smoking 15+ cigarettes/day)		4.5	13.3
Phlegm:					
Men.....	38.0	42.9	42.4	10.7	17.7
Women.....	10.4	(4 of 7 women smoking 15+ cigarettes/day)		5.9	13.3

SOURCE: Huhti, E. (43).

RÉSUMÉ

In all the prevalence studies that have been identified and reviewed, significantly more cigarette smokers consistently reported having symptoms related to chronic respiratory disease. This was true for cough, production of phlegm, wheezing, and shortness of breath. It

was also true when the respondents were asked not about symptoms but about disease, that is, chronic bronchitis and emphysema, and in one instance was reflected in the number of clinic visits for respiratory diseases. Prevalence of these symptoms increased with the amount of cigarettes smoked. It was less among pipe and cigar smokers, and ex-cigarette smokers among whom the prevalence, in some reports, approached that of nonsmokers.

STUDIES RELATING SMOKING TO PULMONARY FUNCTION

Many of the surveys outlined in the previous section on respiratory symptoms also included lung function tests as part of the examination. Huhti (43), for example, in his Finnish study took chest X-rays and collected information on vital capacity, 1-second forced expiratory volume (FEV_{1.0}) and peak expiratory flow (PEF) as shown in table 10.

TABLE 10¹.—Mean values of lung function tests among men and women by smoking habits

	Cigarettes smoked per day			Non-smokers	Ex-smokers
	1-14	15-24	25+		
FEV _{1.0} (liters):					
Men.....	3.17	3.30	3.08	3.46	3.39
Women.....	2.74	(²)	(²)	2.42	2.32
FVC (liters):					
Men.....	4.40	4.51	4.26	4.40	4.51
Women.....	3.53	(²)	(²)	3.18	3.19
PEF (c.c./sec.):					
Men.....	518	537	517	569	551
Women.....	431	(²)	(²)	410	403

¹ Although this table presents data for all ages combined, the same differences were apparent in each 5-year age grouping.

² Only 7 women smoked 15 or more cigarettes per day.

SOURCE: Huhti, E. (43).

Among men the FEV_{1.0} value was lower for smokers than nonsmokers. The PEF value was slightly lower, but the vital capacity was unrelated to smoking. In this study none of the values seemed to be clearly related to the number of cigarettes smoked. Among the relatively small number of female smokers in this study, most of whom smoked between one and 14 cigarettes per day, almost all the lung function values were better than in the female nonsmokers. Female smokers were slightly taller in height and slightly lighter in weight than female nonsmokers, which may account for this finding. However, female ex-smokers had slightly reduced FEV_{1.0} and PEF when compared

with female nonsmokers, similar to the relationship noted between male ex-smokers and male nonsmokers.

Coates (20) observed no relation between smoking habits and vital capacity or $FEV_{1.0}$. He did find, however, that the ratio of $FEV_{1.0}/VC$ was significantly lower among heavy smokers (25 or more cigarettes per day) than nonsmokers. This was found for all but the oldest group of workers, but here the number of subjects was small.

Peters and Ferris (59) asked 133 Harvard College seniors to complete a questionnaire on respiratory symptoms and to perform some sample tests of pulmonary functions. Of these, 124 responded. When classified by smoking history, the smokers were found to record more frequent cough, phlegm production, breathlessness, and wheezing with or apart from colds. There was no difference in vital capacity between smokers and nonsmokers. Although the forced expiratory volume in 1 second ($FEV_{1.0}$) was less for heavy smokers than nonsmokers, this was not significant by itself. As a ratio of vital capacity this did show a significant decrease. The air flow rate using the Wright peak-flow meter and other flow rates determined from tracings of the Stead-Wells spirometer ($FR_{75\%}$, $FR_{50\%}$, $FR_{25\%}$, $FR_{10\%}$) did show statistically significant reductions in heavy smokers as compared to nonsmokers. These data show that relatively young cigarette smokers have some impairments of ventilatory function, in turn suggesting the possibility of a rather immediate effect of cigarette smoking on respiratory symptoms and ventilatory function.

A series of experiments has been done by Krumholz and his associates (49, 50, 51) to evaluate cardiopulmonary function in young apparently healthy persons. The first experiment (49) involved 18 house staff physicians ranging in age from 24 to 37 years. Nine had smoked at least one pack of cigarettes a day for the preceding 5 years and nine had not smoked for at least the same time period. Extensive pulmonary function studies were done at rest and after exercise. The smokers were found to have a greater oxygen debt after exercise, decreased diffusing capacity at rest and with exercise, and decreased total lung capacity and vital capacity.

In the second Krumholz experiment (50) 10 young staff physicians, all of whom had smoked at least one pack a day for 5 years, were given pulmonary function tests immediately after and again 3 weeks after abstinence from smoking. Six physicians refrained from smoking for 6 weeks and were tested again. After 6 weeks of no smoking, expiratory peak flow and pulmonary diffusing capacity were significantly increased. Heart rate and oxygen debt after exercise were decreased. After 6 weeks functional residual capacity was decreased and inspiratory reserve volume and maximal voluntary ventilation were increased.

The final study (51) again used 20 young medical persons divided among 10 smokers and 10 nonsmokers. The mean pulmonary compliance was significantly greater for the nonsmokers than for the smokers.

Since cigarette smokers have a chronically elevated carboxyhemoglobin level, usually greater than 2 percent and occasionally exceeding 10 percent, a study (19) was performed having nonsmokers inhale enough carbon monoxide to raise their carboxyhemoglobin levels to the range seen in a control group of cigarette smokers. This maneuver caused the development, in the study group of nonsmokers, of an increased oxygen debt with exercise and a reduced pulmonary diffusing capacity at rest. These changes after carbon monoxide inhalation were similar to those found without carbon monoxide inhalation when comparing cigarette smokers to nonsmokers. (Further data concerning smoking and carbon monoxide is presented and discussed in the chapter on cardiovascular diseases in this report.)

RÉSUMÉ

Findings from various studies relating smoking to pulmonary function are less consistent for certain criteria of measurement than from those relating smoking to respiratory symptoms. They are, however, consistent in that they all report some form of diminished pulmonary function among cigarette smokers, even when relatively young smokers were studied. This is true of the studies outlined here as well as others that have not been included (18, 40, 56, 58, 81). The usual measurement found to be lower among smokers is the 1-second forced expiratory volume ($FEV_{1.0}$) either alone or as a ratio of the vital capacity ($FEV_{1.0}/VC$). Vital capacity alone was generally not found to be associated with smoking but diminished flow rates, such as FR_{75} , FR_{50} and the peak expiratory flow (PEF), were often observed. In these studies, distinct quantitative relationships were not observed between impairment of pulmonary function and the number of cigarettes smoked daily.

RELATION OF SMOKING TO HEREDITY OR TO CONSTITUTIONAL FACTORS

Although various surveys and studies consistently show an association between smoking and respiratory symptoms and mortality from respiratory disease, there have been objections to interpreting this relation as causal. Arguments have been made that smokers and nonsmokers may differ in some respects, perhaps biological, that are relevant to the occurrence of disease. Others have suggested that pre-

dispositions to smoking and respiratory disease may have a common genetic basis.

One method of trying to estimate the importance of heredity and constitutional factors is to study the effect of tobacco smoking among pairs of twins, particularly identical (monozygotic) twins. If, when one twin in each pair of monozygotic and dizygotic twins is a smoker and the other is not, an excess morbidity does *not* appear among the smoking twins, it would seem that the exposure to tobacco smoke was insufficient to result in greater morbidity. Cederlof and his associates (16, 17) in Sweden studied smoking in relation to morbidity from various causes among 12,889 pairs of twins. Replies to a mailed questionnaire dealing with smoking habits and residential history were received from 10,947 pairs (85 percent). Replies to a second questionnaire with medical questions were received from both members of 9,319 pairs—another response of about 85 percent.

A subject who answered "Yes" to the question, "Do you regularly have a cough?" was regarded as having "cough." If, when asked, "For how many consecutive months a year do you have a cough?", the subject checked more than 3 months, he was regarded as having "bronchitis."

If the group comprising only one of each twin pair (the first twin on the twin registry) is considered as a random population, the association observed between smoking and respiratory symptoms is given in table 11.

TABLE 11.—Prevalence of "cough" and "bronchitis" among smokers and nonsmokers by sex and age

Sex and birth year	Cough		Bronchitis	
	Smoker	Nonsmoker	Smoker	Nonsmoker
Men:				
1886-95.....	17.7	17.8	7.4	5.5
1896-1905.....	15.5	6.6	6.7	2.5
1906-15.....	15.0	5.5	6.3	1.6
1916-25.....	13.8	3.5	4.9	1.2
Women:				
1886-95.....	25.0	8.7	8.3	2.7
1896-1905.....	18.0	7.0	8.0	2.4
1906-15.....	14.2	5.5	4.8	1.4
1916-25.....	11.1	3.8	2.9	.6

SOURCE: Cederlof, R., et al. (17).

These findings are similar to those previously reported for various populations. These respiratory symptoms were then analyzed among twin pairs with discordant smoking habits, that is, one twin of the

pair never smoked and the other either had smoked or still smoked at the time of the survey. The findings are presented in table 12.

TABLE 12.—Prevalence of "cough" and "bronchitis" among smokers and nonsmokers in smoking-discordant twin pairs

Twins	Cough		Bronchitis		Number of pairs
	Smoker	Nonsmoker	Smoker	Nonsmoker	
Monozygotic:					
Men.....	14.6	7.7	6.6	1.1	274
Women.....	13.6	7.6	3.0	2.3	264
Dizygotic:					
Men.....	12.3	5.5	4.5	1.8	733
Women.....	14.5	5.7	5.5	1.8	653

SOURCE: Cederlof, R., et al. (17).

This table shows that the prevalence of respiratory symptoms was much higher among the smokers in twin pairs than the nonsmokers. The authors concluded that this hypermorbidity "speaks in favor of a causal interpretation."

In a further analysis of the data from monozygotic twin pairs with discordant smoking habits, Cederlof and his coworkers (15) divided the series into a "low risk group" in which the nonsmoking twin did not have "cough," and a "high risk group" in which the nonsmoking twin had "cough." The two groups of smoking co-twins corresponding to the two nonsmoking risk groups had higher than expected prevalence rates. The observed value for smokers in the low risk group, however, was only half that expected for nonsmokers in the high risk group. This suggests that for some *individuals* the genetic influence may be more important than smoking in the development of cough. But, because any high risk group is only a small part of the population, the total genetic effect will be much smaller than the effect of tobacco.

Lundman (53) made a detailed study of twin pairs in Sweden. Of 247 twin pairs asked to participate, 196 pairs were examined (80 percent), of which 92 were monozygotic and 104 dizygotic. All participants were interviewed and examined without knowledge of their smoking habits. All twin pairs were concordant with respect to urban/rural residence and discordant in smoking habits. After estimation of lifetime exposure to smoking, 30 pairs were considered concordant, thus limiting analysis to 77 monozygotic and 89 dizygotic pairs. The smokers in both groups of twins had significantly higher frequencies of some respiratory symptoms, such as persistent cough and morning phlegm, but not of other symptoms such as dyspnea, "day cough", and "day phlegm". Smokers also had "an increase in the unevenness of

ventilation measured by nitrogen washout, and an increase in airway resistance as measured by dynamic spirometry."

RÉSUMÉ

Two recent studies (17, 53) of populations of identical and fraternal twins show that for some individuals in the populations studied a genetic element appears to be of some importance for the development of cough. However, the effect of smoking was clearly shown to be much more important for most of the individuals in the total populations studied. One study (53) also clearly showed that smoking twins more often had reduced ventilatory function tests as compared to their respective nonsmoking twins.

These data provide strong confirmatory evidence that cigarette smoking can cause chronic bronchitis; however, no inferences with respect to pulmonary emphysema can be based on these data. Studies such as these, when specifically designed to provide additional information about pulmonary function, may be helpful in evaluating the relationship between cigarette smoking and pulmonary emphysema.

PATHOLOGY STUDIES

Very few papers relating the gross and microscopic appearance of the trachea, bronchi, and lung parenchyma to tobacco smoking have appeared in the last 3 years. Auerbach and his coworkers have continued their analysis of bronchial tissues taken from 758 subjects (7) and lung parenchymal tissue taken from 1,340 men (8). They published a report (9) correlating findings in the bronchial tree with findings in the lung parenchyma of 267 men who were included in both previous studies. They reported a high correlation between fibrosis in the lung parenchyma and different abnormalities of the bronchial epithelium, such as hyperactive glands, increased number of cell rows in the ciliated epithelium, and increased frequency of cells with atypical nuclei. As reported previously by and summarized in the Surgeon General's 1964 Report, more frequent and more severe abnormalities were observed among cigarette smokers. Sections of the bronchial tree among ex-smokers were more like those of nonsmokers while fibrotic changes in the lung parenchyma were more like those observed among smokers.

Changes in the bronchial tree similar to those described by Auerbach and his coworkers were reported in a series of 100 random adult autopsies by Hernandez and Anderson and their associates (38). They reported a higher frequency of abnormal epithelial hyperplasia, goblet cell hyperplasia, round cell infiltration, congestion, and edema in

bronchi from smokers than nonsmokers. There was, however, no evidence of more bronchial gland hyperplasia.

These same workers also studied macroscopic sections of single lungs from 211 routine autopsies on adults (1, 2). Analysis was limited to 165 of these cases on whom smoking histories were obtained, usually from relatives. Without knowing the identity of the subject or his smoking history, each lung section was classified on a scale from 0 to 6 by severity of emphysematous changes. The type of emphysema was also described as panlobular (changes throughout the secondary pulmonary lobules), centrilobular (changes located around the centers of the secondary lobules), or mixed. The severity of emphysematous changes was about the same for men and women, but for each sex, changes were more severe among smokers than nonsmokers, as seen in table 13.

TABLE 13.—*Mean severity of emphysema classified by macrosections by sex and smoking history*

	Number	Mean degree of emphysema		Number	Mean degree of emphysema
Men:			Women:		
Smokers.....	96	2.3	Smokers.....	18	2.1
Nonsmokers....	11	1.1	Nonsmokers....	40	.8

SOURCE: Anderson, A. E., Jr., et al. (8).

Perhaps more important was the observation that the type of pathology seemed strongly related to smoking (2). Of 48 subjects whose lung macrosections were classified as having mainly centrilobular emphysema, 45 persons had been smokers. In contrast, the 62 subjects judged to have panlobular emphysema were divided in the expected proportions, 38 smokers and 24 nonsmokers.

Petty and his associates (61) also studied postmortem findings in the lungs of a series of 253 men over age 40, unselected for smoking, who died in two Denver hospitals during a 6-year period from 1959 to 1965. The presence and severity of emphysema was estimated and graded in four categories, from 0 to 3+. During the last 3 years of the study bronchi of 179 men were examined for mucous gland hyperplasia. Independent of the morphological studies, smoking histories were obtained for each person, apparently by questioning relatives, although this is not clearly stated. Men were grouped according to the amount of cigarettes smoked during their lifetimes by calculating pack-years of smoking. (One pack-year is the number of cigarettes smoked if a person smoked one pack per day for a year. A pack-year could also mean smoking two packs a day for 6 months, one-half pack a day for 2 years, or any equivalent amount.)

Of the group of 179 individuals, 54 had mucous gland hyperplasia. Of the 54 persons involved, 51 had smoked more than 20 pack-years, and the remaining three were essentially nonsmokers. In contrast, approximately one-third of the 125 men in whom mucous gland hyperplasia was not found were essentially nonsmokers. When the total group of 253 men was studied for evidence of pulmonary emphysema, 114 were found to have moderate or severe pulmonary emphysema. Of the 114, 98 had smoked more than 20 pack-years. The other six, who essentially were nonsmokers, had either asthma, previous tuberculosis, deep-seated lung infections or other demonstrable relationships with previous pulmonary disease. In contrast, approximately one-third of the remaining 139 men, who had either very mild or no emphysema, were essentially nonsmokers.

Only one study has been found in which the frequency of abnormal bronchial epithelial cells in living persons is compared with smoking history. Robbins (63) studied a group of 103 college students between the ages of 17 and 24. Of the 45 who had never smoked, atypical epithelial cells were found in six (13 percent). This compares to 26 (45 percent) of the 58 students who had been smoking 10 or more cigarettes daily for 1 to 8 years. Cytological examination was done without knowledge of whether the specimen came from a smoker or nonsmoker.

ANIMAL EXPERIMENTS

Results of two experimental studies relating smoke inhalation to lung parenchymal changes in dogs have been published in the last 3 years. Hernandez and his coworkers (39) used 23 healthy greyhounds retired from racing. Eight served as controls and 15 were exposed to high concentrations of cigarette smoke for 30-45 minutes twice daily in wooden inhalation chambers. Seven animals were exposed for approximately 5 months and the remaining eight were sacrificed after almost 15 months of smoke inhalation. Disruption of the lung parenchyma was assessed macroscopically by comparison with preselected standards graded in severity from 0 to 3. Assessment was made without knowledge of the source of the lung specimen. Lung damage among dogs that were exposed longer showed significantly greater disruption of the lung parenchyma.

Auerbach and his associates (5, 6) tracheostomized 10 adult beagles and, in an attempt to approximate human smoking more closely, exposed them to cigarette smoke through the tracheostomy tube. Five dogs died during this experiment and the remaining five were sacrificed after approximately 14 months of exposure. Other beagles

were kept as controls; two had tracheostomy openings. These control dogs were sacrificed at the time the last five smoking dogs were sacrificed. Lungs of the dogs exposed to cigarette smoke showed microscopically the presence of dilated air spaces, especially beneath the pleural surface. Here the alveolar septa showed a fibrous thickening of the walls with areas of rupture and dilated air sacs. Padlike attachments to alveolar septa were found. These zones of connective tissue surrounding dilated air sacs were also visible macroscopically as white areas on the lung surface. There was no thickening of the walls of small arteries and arterioles within the lung. The lungs of the control dogs were normal in appearance with none of these changes. These abnormalities approximate but are not fully concordant with some of the typical pathological findings in human emphysema. This experiment does indicate that inhaled cigarette smoke apparently can damage the pulmonary parenchyma of dogs. Other findings (6) as yet unpublished, indicate that abnormalities of the bronchial epithelium resulted that approximate many of the histopathologic findings of human chronic bronchitis.

Rockey et al. (64) have noted that cigarette smoke produces bronchial and parenchymal changes in dogs that approximate some of the histopathologic findings found in human smokers who have chronic bronchitis and/or pulmonary emphysema. Mouzakis (57) has noted similar changes in rabbits, and in dogs exposed to cigarette smoke through tracheostomies.

RÉSUMÉ

Researchers carrying out pathological studies have consistently reported epithelial hyperplasia of the bronchial tree associated with smoking. They have also reported that fibrosis and emphysematous changes in the lung parenchyma, although observed among non-smokers, occur much more frequently among men and women who have histories of smoking. Changes in the lung parenchyma, approximating some of the changes noted in human emphysema, have also been produced experimentally in dogs by exposure to cigarette smoke.

CILIATOXIC EFFECTS OF CIGARETTE SMOKE

The toxic effect of tobacco smoke on the ciliary defense mechanism of the respiratory system has been confirmed by additional experimental studies (9, 10, 13, 23, 24, 26, 27, 45, 47, 77, 78) which seek to determine more exactly the mode of action of the ciliatotoxic agents contained in tobacco smoke. As yet, hydrogen cyanide and acrolein appear to have the greatest ciliatotoxic effects of the agents that have been identified in the gaseous phase of tobacco smoke, although for-

maldehyde, crotonaldehyde, formic acid, acetic acid, propionic acid, and some phenols are also ciliotoxic (25, 46, 48, 73, 77, 79). Further information may be obtained from a special symposium on ciliary activity held in 1965 (48). A recent study (22) suggests that oxidative enzymes such as adenosine triphosphatase, apparently important to ciliary activity, may be adversely affected by cigarette smoke. Additional research is necessary before precise conclusions can be stated concerning which, if any, of the identified ciliotoxic agents contained in tobacco smoke are most damaging to the human respiratory system.

OTHER FACTORS ASSOCIATED WITH CHRONIC BRONCHITIS OR EMPHYSEMA OR BOTH

It is not the purpose of this report to discuss all the factors that may play a role in the development of chronic bronchitis and emphysema. It is important, however, to recognize that these conditions do exist among people who do not smoke and that many smokers apparently escape all signs of affliction. It is also important to recognize that other factors have been associated with the development of chronic respiratory disease, or chronic bronchitis and emphysema, as we have defined chronic respiratory disease. We must be concerned with the multiple etiology of biological processes. One factor already cited is the role of hereditary or constitutional factors in the development of respiratory symptoms, either operating alone or in conjunction with other factors such as smoking.

Aside from the personal pulmonary pollution inherent in smoking, occupational exposures (a wider form of pollution) and exposure to various pollutants in the atmosphere have both been shown to influence the prevalence of respiratory signs and symptoms. Studies made in some specific industries—for example, pulp mill workers in New England (32), coal miners in West Virginia (31), and gold miners in South Africa (66, 67)—have shown an increased frequency of respiratory symptoms or of diminished pulmonary function among men exposed to certain dusts and fumes.

These studies indicate that cigarette smoking is generally more important than the occupational exposures in producing respiratory disease in the workers. These studies also suggest that cigarette smoking may interact with some occupational exposures to produce even greater deleterious effects. Cigarette smokers outnumber by far the workers subjected to unusual environmental exposures. Also, there has been a general improvement in many occupational environments, in the continuing effort to remove or reduce the exposure to specific industrial air pollutants.

Climatic and meteorologic variations involved with differences in quantity and quality of specific air pollutants make investigations of atmospheric pollution very complex. There have been many studies, however, attempting to examine the association of air pollution with chronic respiratory disease. Often comparisons of mortality and morbidity are made between urban and rural areas, assuming a difference in air pollution but not measuring it directly. Wicken (75) in his retrospective study of mortality from chronic bronchitis in Northern Ireland found higher mortality rates with greater degrees of urbanization. Air pollution was suggested as a factor.

Holland and Reid (42) compared the prevalence of respiratory symptoms, sputum production, and lung function in London and in three county towns. The London men had more and severer symptoms, produced more sputum and had poorer lung function test results. Smoking habits were shown to be closely related to respiratory disturbance but urban-rural differences in these habits could not explain the greater frequency of respiratory symptoms in London.

A Canadian study reported by Bates et al. (11) indicates that among four cities studied, the city with the lowest amount of industrial dust-fall and sulfur dioxide levels had the study group with the lowest prevalence of chronic bronchitis. Preliminary results also indicate that this group had the lowest decline of pulmonary function. The groups of males in each city were approximately concordant for other factors, including the influence of cigarette smoking.

Ferris and associates (3, 4, 33) studied air pollution and its effect on respiratory symptoms and functions in two separate towns—Chilliwack, British Columbia, and Berlin, N.H. After standardizing the data for age and cigarette smoking, they observed a correlation between symptoms of chronic bronchitis and the level of air pollution as measured by the mean sulfation rate. They also found pulmonary function tests to be better in Chilliwack when controlled for smoking habits and age. This may be associated with the lower level of air pollution in Chilliwack.

Studies of populations of twins are especially valuable in assessing the influences of constitutional factors and environmental considerations, such as cigarette smoking and air pollution. Cederlof (14), using interview techniques on a large population of twins in Sweden, found that compared with smoking, air pollution was of secondary importance in causing respiratory symptoms indicative of chronic bronchitis and/or emphysema. In both the monozygotic and dizygotic twins, again using the co-twin control method, individual variations suggested that the propensity to develop cough from smoking also may well be pertinent with regard to air pollution but that, when considering the total population, individual variations appear to be of minor influence (15).

Other studies (55, 76) have suggested a relation between air pollution and symptoms or mortality from chronic respiratory disease, although they were not controlled for differences in cigarette smoking.

The contributions of air pollution, industrial pollution, and personal pollution have been summarized recently by Higgins (40). He concluded, as we must from the available evidence, that all "* * * three types of pollution are associated with increased amounts of respiratory disease and respiratory disability." All the recent evidence, however, does not alter the conclusion in the Surgeon General's 1964 Report that "the dominant association in the United States is between cigarette smoking and chronic respiratory disease."

ADDITIONAL CONSIDERATIONS REGARDING SMOKING AND EMPHYSEMA

This crucial question must be answered affirmatively before an inference can be made that smoking directly causes pulmonary emphysema: Does inhaled tobacco smoke have a direct toxic effect on the alveolar tissue in the lung parenchyma which is important in the pathogenesis of pulmonary emphysema? At present, it cannot be answered.

If future evidence supports such a finding of a direct toxic effect, we will have the missing link to the present chain of evidence showing a strong association between cigarette smoking and many cases of pulmonary emphysema and an inference of causation may validly be made. The available evidence that follows has only indirect pertinence to the question.

The experiments of the Auerbach, Hernandez, and Rockey groups support the thesis that there is a direct toxic effect of cigarette smoke on the pulmonary tissue. Possibly this direct toxic effect, if proven to exist, contributes to the rupture and fibrosis of the alveolar tissue. However, in these animal studies there were also some differences from the typical anatomic findings of human pulmonary emphysema.

Surfactant, a fluid substance lining the alveolar cell walls, apparently is important for maintaining tissue surface tension and thus the spatial configuration of the alveolar walls (65). *In vitro* abnormalities have been noted in surfactant as a result of cigarette smoke (21, 74). Alveolar macrophages (specialized cells that incorporate and remove foreign material from the affected lung area) are reportedly damaged *in vitro* by cigarette smoke (35). Abnormalities of the alveolar macrophages and lipophages with inhalation of cigarette smoke are also reported (54) in cytological studies of human bronchial washings, apparently reflecting damage *in vivo*.

Studies (49, 50, 51, 62) of the pulmonary function of relatively young smokers and nonsmokers also indicate that abnormalities of pulmonary diffusion noted in cigarette smokers, may, in part, be related to a direct toxic effect of cigarette smoke. However, some of these abnormalities are related to the unevenness of pulmonary ventilation associated

with airway abnormalities. Damage to the pulmonary arterial capillaries has frequently been noted on autopsy examination of smokers. This damage may be a direct effect of smoke inhalation and, functionally, may impair the vascular perfusion of the alveolar tissue, thus leading to further deficiencies in alveolar tissue function.

The possibility must also be considered that the accelerated *in vitro* thrombus formation (discussed in the cardiovascular chapter of this report), associated with cigarette smoking, may be the basis for multiple small thromboses in the pulmonary arterial capillaries.

Additional research is also needed to answer questions concerning other factors that may account for the apparent increased susceptibility of some individuals to cigarette smoke, such that they have a marked excess mortality from this disease. Genetic and constitutional factors may be important to some individuals' development of pulmonary emphysema, just as these factors appear to be important in the development of cough in smokers, as reported by Cederlof and his associates (14, 15, 16, 17). An increased susceptibility of some individuals to the emphysema associated with cigarette smoking has been suggested, but not proved, by the occasional reports of "familial" emphysema (41, 52).

Other probable causes of pulmonary emphysema, such as allergic or infectious disease processes, also should be investigated for interactions with and without smoking. Other apparent causes of pulmonary emphysema, such as possibly atmospheric air pollution, may be interacting with cigarette smoking to produce effects even more deleterious to human health.

The observation that other probable causes of pulmonary emphysema may exist should not detract from the strong relationship that has been shown to exist between cigarette smoking and pulmonary emphysema. Further investigations of the mechanisms of injury to the cellular and subcellular structures of the lung tissue are recommended (34). Also, clarification of diagnostic nomenclature and criteria would be helpful, as indicated in the earlier discussion of definitions in this chapter.

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CHAPTER 3

Smoking and Cancer

CONTENTS

	Page
General Chemical and Experimental Data on Carcinogenesis and Tobacco Smoke.....	127
<i>In Vitro</i> Cellular Changes by Tobacco Smoke.....	129
<i>In Vivo</i> Tumor Formation by Tobacco Smoke.....	129
Tumor-Promoting Agents in Tobacco Products.....	130
Lung Cancer.....	131
Mortality Data.....	131
Histopathology of Lung Tumors.....	140
Experimental Pulmonary Carcinogenesis.....	144
Additional Evidence Concerning Experimental Carcinogenesis.....	144
Cancer of the Buccal Cavity and Pharynx (Lip, Mouth, Throat).....	145
Cancer of the Larynx.....	148
Cancer of the Esophagus.....	149
Cancer of the Urinary Bladder.....	153
Cancer of the Stomach.....	157
Cancer of the Pancreas.....	158
Cited References.....	161
Supplemental References.....	167

GENERAL CHEMICAL AND EXPERIMENTAL DATA ON CARCINOGENESIS AND TOBACCO SMOKE

Polynuclear Aromatic Hydrocarbons

As criteria for the presence of polynuclear aromatic hydrocarbons in tobacco smoke, the list of J. W. Cook (20) has been widely accepted by tobacco chemists.

The Surgeon General's 1964 Report and Cook's paper are in agreement with respect to the presence of benzo(a)pyrene (3:4-benzopyrene), dibenz(a,h)-anthracene (1,2:5,6-dibenzanthracene),¹ benzo(c)phenanthrene (3:4-benzophenanthrene), and dibenzo(a,i)pyrene (3,4:9,10-dibenzopyrene), all having carcinogenic activity.

Cook considers, furthermore, as identified: Benz(a)anthracene (1,2-benzanthracene) marginal carcinogenic activity; chrysene, benzo(e)pyrene (1,2-benzopyrene), questionable carcinogenic activity; benzo(g,h,i)-perylene (1,12-benzoperylene),² benzo(b)fluoranthene (3,4-benzofluoranthene) carcinogenic (59, 106), and benzo(j)fluoranthene (10,11-benzofluoranthene) carcinogenic (106).

Indeno (1,2,3-cd)pyrene (2,3-phenylenepyrene) has since been isolated from tobacco smoke (45). This polynuclear aromatic hydrocarbon was found to be carcinogenic (44, 59). The following carcinogens, or questionable carcinogens, were isolated by Kiryu and Kuratsune (55) in the smoke of cigarettes smoked by human volunteers: benz(a)anthracene, chrysene, benzo(a)pyrene, benzo(e)pyrene, benzo(b)fluoranthene and benzo(k)fluoranthene. The carcinogenic polynuclear aromatic hydrocarbons are regarded as the major initiating carcinogens in tobacco smoke.

N-Heterocyclic Aromatic Hydrocarbons

The Surgeon General's 1964 Report lists as carcinogenic compounds three N-heterocyclics, dibenz(a,j)acridine, dibenz(a,h)acridine and 7H-dibenzo-(c,g)carbazole. An independent investigation has confirmed the presence of the first named compound in cigarette smoke (107).

N-Nitrosamines

N-nitrosamines are among the most powerful known animal carcinogens. Since tobacco smoke contains secondary amines (57, 71)

¹ Dibenzo (a,h)anthracene in the Surgeon General's 1964 Report should be replaced by dibenz(a,h)anthracene (24).

² Benzo(g,h,i)perylene was not tested for carcinogenicity until 1966 and then was found to be inactive (44).

and most tobaccos, certainly Burley and Maryland varieties, contain nitrates (64), tobacco smoke can be considered as a potential environment for the formation of N-nitrosamines. The major nitrates in tobacco are alkaline nitrates.

Neurath, et al., isolated three aliphatic N-nitrosamines from the smoke of a cigarette rich in volatile basic components and high in nitrate content. One of them tentatively has been identified as methyln-butyl-nitrosamine (73).

When the particulate matter, "tar," was collected from cigarettes not enriched with basic components or when the smoke particulate matter was collected without aging and not in cold traps, N-nitrosamines could not be isolated from cigarette smoke (72). Since the only other publication concerned with the isolation of nitrosamines in cigarette smoke was based on cold trap collection of "tar," the positive finding of three N-nitrosamines appears questionable (86).

In summary, tobacco smoke can be regarded as a potential environment for the formation of N-nitrosamines. However, additional information is needed to substantiate their presence in tobacco smoke.

Polonium 210

Several investigators (33, 35, 50, 76, 92, 93, 112) have found trace amounts of Po^{210} in tobacco leaf and cigarette smoke. The concentration of Po^{210} in lung tissue is relatively high (33, 67) as compared to other body tissues and is higher in smokers than in nonsmokers (33, 43, 65, 66).

Lung tumors have been induced experimentally by intratracheal implantation of various radioactive substances. These radioactive substances must, however, be present in the respiratory environment above a certain threshold level and must be in contact with the target organ long enough to be effective (68, 77, 88, 107). Because Po^{210} emits alpha particles, it has been implicated as a lung cancer initiator (43, 68, 76, 77). More research is needed before definitive conclusions can be made. Until such time, however, Po^{210} should be considered as a potential tumor initiator in tobacco smoke.

Selenium

Selenium has been mentioned as possibly being important in the pathogenesis of human lung cancer (100). Preliminary reports suggest that selenium may be present in some cigarette papers. Because earlier reports (17, 34, 97) indicated the ingestion of selenium caused cancer of the liver in mice, a recent investigation (101) by the National Cancer Institute was conducted, with negative results. So far the earlier reports of the carcinogenicity of selenium have not been substantiated. Additional information is needed on the possible carcinogenicity of selenium and its presence in cigarette smoke before selenium can be indicted as an agent in human cancer.

Phenols

Tobacco smoke contains a large number of phenols (107). Several of them are known to be tumor promoting agents when applied in high concentrations to mouse skin previously treated with a tumor initiator (14).

IN VITRO CELLULAR CHANGES BY TOBACCO SMOKE

Lasnitzki (60) extended her studies with tobacco smoke condensate on cultured human fetal lung tissue to include a "highly purified fraction of hydrocarbons" isolated from cigarette smoke condensate. In 33 out of 50 treated lung tissue explants, the epithelium of the bronchi was hyperplastic and sometimes showed squamous changes. These changes were not observed with the untreated controls. Although a hydrocarbon-free fraction was weakly active by producing some squamous metaplasia in these explants, these tissue culture tests point strongly to carcinogenic hydrocarbons as the active group in the smoke. The findings with purified carcinogenic hydrocarbons in organ culture (21) support the finding that polynuclear aromatic hydrocarbons are one group of active smoke constituents. Carcinogenic hydrocarbons are also the only group of chemical components that have been demonstrated *in vitro* to induce malignant conversion of single cells (7, 13).

In summary, tobacco smoke has been demonstrated *in vitro* to induce pathological changes in tissue explants. Although such changes may be induced by different smoke constituents, as yet the carcinogenic hydrocarbons are the only agents identified in tobacco smoke which have been shown to induce malignant changes in tissue cultures.

IN VIVO TUMOR FORMATION BY TOBACCO SMOKE

Passive inhalation experiments with tobacco smoke have not yet led to fully established squamous carcinoma in mice (109). This method of application has resulted only in papillomatous growth in the tracheobronchial mucosa of a few hamsters. None of the tumors, however, was found to be invasive (30, 111). It appears that passive inhalation may not lead to the induction of squamous cell bronchogenic cancer in experimental animals. This conclusion can also be applied to passive inhalation studies in which the animals are infected by a virus before long-term smoke exposure (62, 110). The pathological changes seen in the mice were reversible whether or not the animals were previously infected with a virus. The hyperplasia and metaplasia seen in mice and rats after passive inhalation appears, at least in part, to be secondary to viral or bacterial infection that is enhanced by exposure to tobacco smoke. The relatively negative findings with pas-

sive inhalation experiments probably relate to the relatively small amounts of smoke aerosols that bypass the nasal passages. The defensive nature of the upper respiratory tract against airborne irritants has to be fully appreciated in the evaluation of any passive inhalation study.

Active inhalation studies with tracheostomized dogs, as carried out by Rockey, (79, 80) and Auerbach (2), suggest that this approach may lead to the induction of bronchogenic carcinoma. The change in the bronchial epithelium after 1 year of active smoking indicates early pathological changes that may, upon continued smoke exposure, lead to tumors in the bronchi.

So far, neither passive nor active inhalation studies have contributed to our knowledge about the nature of the tobacco smoke carcinogens. Studies with the particulate matter, tar, of cigarette, pipe, and cigar smoke, however, have clearly demonstrated that at the site of application tumors can be induced. Tumors have been induced on the skin of mice and rabbits, the ears of rabbits, the subcutaneous tissue and hilum of rats and the cervixes of mice (9, 11, 22, 31, 32, 46, 48, 61, 74, 82, 83, 84, 107, 108).

Only relatively few investigators have been concerned with the nature of chemical carcinogens in tobacco smoke (47, 84, 107). Although the acidic and nicotine-free basic portions of tobacco tar had been found to have weak tumorigenic activity, the only fraction shown to have induced significant numbers of tumors is fraction B of the neutral portion (2 percent of the whole condensate) (107). This B fraction was further fractionated into three subfractions from which only B₁ was shown to have tumorigenic activity (47). The B₁ fraction equals 0.6 percent of the tar and combines all aromatic hydrocarbons with three to seven rings including the carcinogenic ones. This can be considered as evidence that in *in vivo* studies, the polynuclear aromatic hydrocarbons are the major carcinogens in tobacco smoke. Although these compounds alone can account for only a small portion of the tumorigenic activity of tobacco tar, they are, nevertheless, the only identified carcinogens and tumor initiators in tobacco smoke shown by experimentation to be biologically active. Their tumorigenic effect is enhanced by the presence of tumor-promoting agents in the smoke.

TUMOR-PROMOTING AGENTS IN TOBACCO PRODUCTS

In the experimental setting, the tumorigenicity of tobacco smoke condensate cannot be solely explained by the presence of known carcinogens. In assays on mouse skin and rat subcutaneous tissue, the known carcinogens must be enhanced by other components such as tumor-promoting agents. In fact, it has been demonstrated that to-

bacco extract and tobacco smoke condensate can act as promoters to mouse skin previously treated with tumor-initiating carcinogenic polycyclic aromatic hydrocarbons (10, 12, 96, 107). Although some tumor-promoting activity of tobacco "tar" can be explained by some phenols and carboxylic acids, additional tumor promoters in tobacco products remain to be isolated and identified.

It is important, however, that a significant decrease of the polynuclear aromatic hydrocarbons in tobacco "tar" leads to a significant decrease of the overall activity of the "tar" on mouse skin (9, 46, 108, 109).

In summary, experimental studies have demonstrated that the particulate matter of tobacco smoke, "tar," is tumorigenic. Some polynuclear aromatic hydrocarbon-carcinogens have been identified as contributing significantly to the overall tumorigenic activity of tobacco smoke condensates in the experimental setting.

LUNG CANCER

MORTALITY DATA¹

The annual number of deaths in the United States from cancer of the lung (International Classification of Diseases, Codes 162, 163) rose from 18,313 deaths in 1950 to 45,838 in 1964 (94). In this 15-year period, deaths from lung cancer totaled 467,442. During this same time period the death rate for cancer of the lung almost doubled, a rise from 12.2 deaths per 100,000 population in 1950 to 24 deaths per 100,000 population in 1964. (The corresponding age-adjusted rate has also nearly doubled, therefore the increase in the death rate cannot be attributed to the changing age composition of the population.) The lung cancer mortality in the male population increased from 19.9 deaths per 100,000 population in 1950 to 41.4 in 1964, while in the female population the deaths increased from 4.5 to 7.1 per 100,000 population over the same time period.

The mortality experience of the individual male cohorts during 1949-64 (fig. 1) shows that at any given age the risk of dying from lung cancer was almost always higher for the more recently born cohort. Within each cohort, the death rate for lung cancer increased steadily to the end of the life span.

Figure 2 shows the death rate for women by cohort groups and age at death. One can see the increasing death rate slope for each more recently-born cohort, starting with cohort F—those women who were 26-30 years old in 1930. This corresponds to the time when smoking became increasingly popular among women.

¹ All death rates throughout this chapter are per 100,000 population unless otherwise indicated.

Source: National Center for Health Statistics (9f).

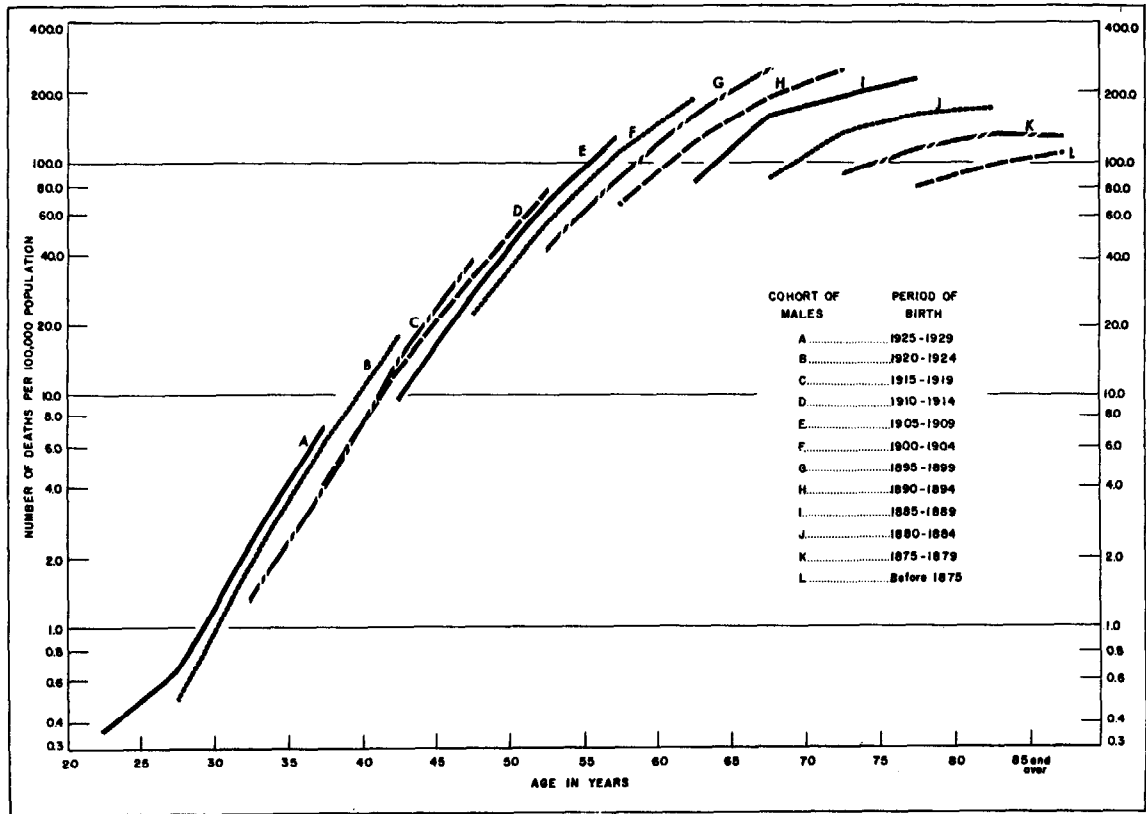


FIGURE 1.—Cancer of the lung among men, by birth cohort and age at death: 1949, 1954, 1959, and 1964.

Source: National Center for Health Statistics (94).

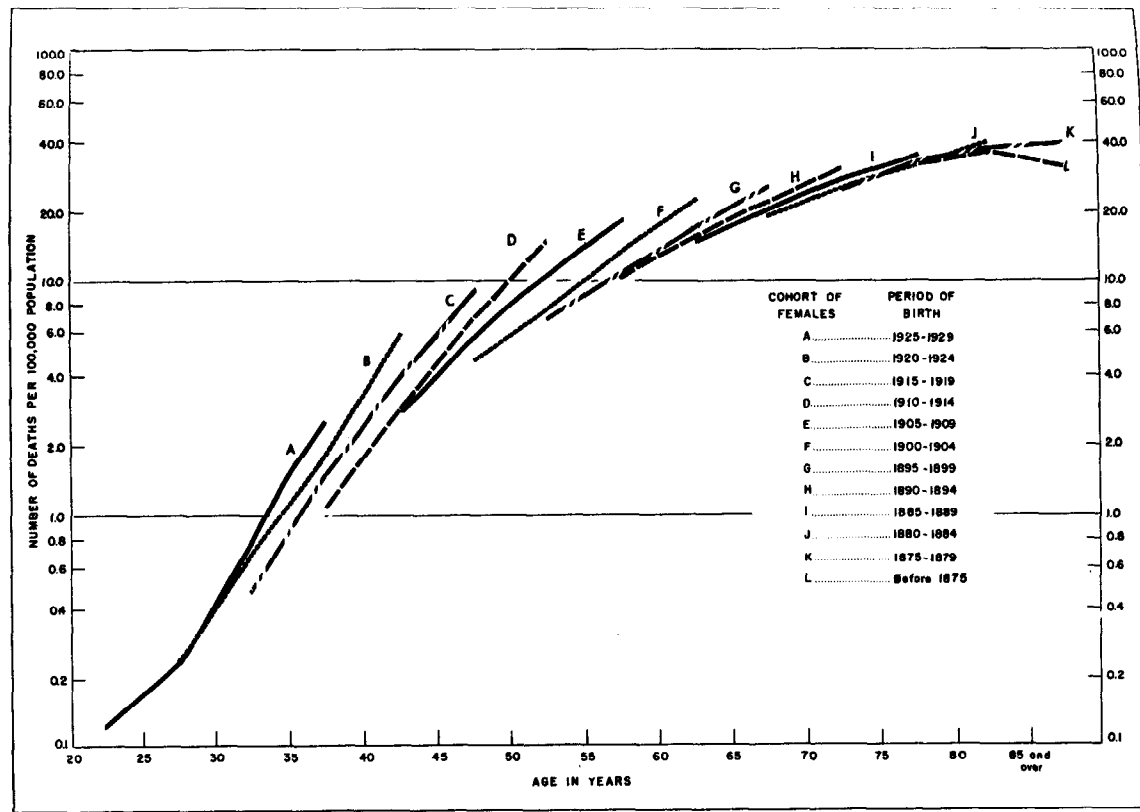


FIGURE 2.—Cancer of the lung among women, by birth cohort and age at death: 1949, 1954, 1959, and 1964.

In the female population the greatest percentage increase (116 per cent) over the 15-year period, 1949-64, occurred in the 35-44 year age group. The next highest percentage increase was noted in the age group 45-54 years. The death rate from lung cancer among women, 25 years and over, rose steadily with advance in age for each year during 1950-64, and the cohort experience shows that these death rates continued to increase for each cohort to the end of the life span.

Hammond's (40) prospective study provides extensive information about the lung cancer mortality experience of both men and women in relation to cigarette-smoking history as presented by mortality ratio¹ and by death rates per 100,000 person-years. (Table 1).

TABLE 1.—Lung cancer mortality ratios and death rates* of smokers by sex and specific age groups

	45-64 years		65-70 years	
	Females	Males	Females	Males
Mortality ratios.....	2.17	7.84	¹ 1.76	11.59
Death rates.....	² (7)15	² (11)87	² (17)30	² (25)262

¹ Computed from app. table 19.

² Numbers in parentheses indicate death rate for nonsmokers.

SOURCE: Hammond, E. C. (tables 24 and 26, app. table 19 (40)).

Tables 2 and 3 below show the relationships of number of cigarettes smoked per day, degree of inhalation, and age smoking began, to lung cancer mortality ratios and death rates for males and females, respectively. Generally, mortality ratios and death rates increase with increasing amount of cigarettes smoked and degree of inhalation, and with a longer lifetime history of smoking. Table 3 shows the relatively lower lung cancer mortality among women as contrasted to men, but reveals, for the most part, the same relationship to amount smoked, degree of inhalation, and age when smoking began.

Table 4 illustrates the fact that cessation of cigarette smoking is associated with a decline in lung cancer death rates.

* The mortality ratio is the ratio of the death rate of smokers to that of nonsmokers—the mortality ratio of nonsmokers always being one, by definition.

TABLE 2.—*Lung cancer (men). Number of deaths, and age-standardized death rates and mortality ratios, by current number of cigarettes smoked per day, degree of inhalation, and age began smoking, by age at start of study*¹

Number of cigarettes a day, degree of inhalation, and age began smoking	Age 35-54		Age 55-69		Age 70-84		All ages, 35-84	
	Number of deaths	Death rate	Number of deaths	Death rate	Number of deaths	Death rate	Number of deaths	Death rate
Current number of cigarettes a day:								
1 to 9.....	9	38	12	68	5	134	26	56
10 to 19.....	15	24	57	168	10	243	82	90
20 to 39.....	138	88	216	264	27	446	381	169
40 plus.....	26	47	50	334	6	754	82	201
Degree of inhalation:								
None or slight.....	19	29	87	203	14	193	120	102
Moderate.....	114	52	177	224	20	401	311	133
Deep.....	55	55	73	266	13	638	141	173
Age began cigarette smoking:								
25 or older.....	5	17	12	65	3	85	20	39
20 to 24.....	31	36	72	212	7	306	110	118
15 to 19.....	112	84	176	250	27	490	315	155
Less than 15.....	35	79	87	302	9	424	101	183
Never smoked regularly.....	11	6	27	19	11	25	49	12
Lung cancer mortality ratios (men)								
Current number of cigarettes a day:								
1 to 9.....		6.17		3.53		5.32		4.60
10 to 19.....		3.90		8.77		9.62		7.48
20 to 39.....		9.37		13.82		17.62		13.14
40 plus.....		7.67		17.47		29.84		16.61
Degree of inhalation:								
None or slight.....		4.75		10.60		7.65		8.42
Moderate.....		8.48		11.72		15.88		11.45
Deep.....		9.00		13.93		25.28		14.31
Age began cigarette smoking:								
25 or older.....		2.77		3.39		3.38		3.21
20 to 24.....		5.83		11.11		12.11		9.72
15 to 19.....		8.71		13.06		19.37		12.81
Less than 15.....		12.80		15.81		16.76		15.10

¹ Mortality ratios are based on death rates carried out to 1 more significant figure than shown.

SOURCE: Hammond, E. C. [table 20 (40)].

TABLE 3.—Lung cancer (women). Number of deaths, age-standardized death rates, and mortality ratios, by type of smoking (lifetime history), current number of cigarettes smoked per day, degree of inhalation, and age began smoking, by age at start of study ¹

Type of smoking (lifetime history)	Age 40-54		Age 55-74		All ages, 40-74	
	Number of deaths	Death rate	Number of deaths	Death rate	Number of deaths	Death rate
Never smoked regularly.....	25	4	77	12	102	7
History of cigarette smoking.....	48	11	33	23	81	16
Current regular cigarette smoking						
Current number of cigarettes a day:						
1 to 19.....	15	8	5	7	20	8
20 plus.....	28	17	22	50	50	36
Degree of inhalation:						
None or slight.....	16	13	9	13	25	13
Moderate or deep.....	27	11	18	48	45	27
Age began smoking:						
25 or older.....	7	6	16	21	23	12
Less than 25.....	35	14	11	43	46	27
Lung cancer mortality ratios (women)						
Never smoked regularly.....		1.00		1.00		1.00
History of cigarette smoking.....		2.82		1.93		2.20
Current regular cigarette smoking						
Current number of cigarettes a day:						
1 to 19.....		2.08		0.62		1.06
20 plus.....		4.43		4.91		4.76
Degree of inhalation:						
None or slight.....		3.33		1.12		1.78
Moderate or deep.....		2.90		4.04		3.70
Age began smoking:						
25 or older.....		1.55		1.76		1.70
Less than 25.....		3.78		3.60		3.65

¹ Mortality ratios are based on death rates carried out to 1 more significant figure than shown.

SOURCE: Hammond, E. C. [table 23 (40)].

TABLE 4.—Lung cancer (men). Age-standardized death rates and mortality ratios for ex-cigarette smokers with a history of cigarette smoking only, by former number of cigarettes smoked per day, and years since last cigarette smoking. Death rates for current cigarette smokers with a history of cigarette smoking only. Men who never smoked regularly are shown for comparison. Men aged 50–69.

Ex-cigarette smokers (years since last cigarette smoking)	Smoked 1–19 cigarettes a day			Smoked 20+ cigarettes a day			Mortality ratio, smoked—	
	Number of men	Number of deaths	Death rate	Number of men	Number of deaths	Death rate	1–19	20+
Under 1 year.....	746	3	108	2,244	33	437	-----	-----
1 to 4 years.....	1,844	5	69	5,435	33	180	-----	-----
5 to 9 years.....	1,770	1	15	5,803	22	108	-----	-----
10 plus years.....	4,209	1	6	8,142	5	16	-----	-----
Total ex-smokers.....	8,569	10	30	21,624	93	119	12.0	7.9
Current cigarette smokers.....	22,808	80	97	56,886	351	205	6.5	13.7
Never smoked regularly.....	55,728	32	15	55,728	32	15	-----	-----

¹ Computed from source.

SOURCE: Hammond, E. C. (table 21 (40)).

The Dorn study (49) of U.S. veterans provides additional information on the relationship of dosage to mortality ratios and death rates for males who smoked cigarettes only (table 5).

TABLE 5.—Lung cancer mortality ratios and death rates for U.S. veterans by age, type, and amount of smoking

	Number of cigarettes/day									
	0		1–9		10–20		21–39		40+	
	DR ¹	MR ¹	DR	MR	DR	MR	DR	MR	DR	MR
Current cigarette smokers only:										
Age 45 to 54.....					24		52		72	
Age 55 to 64.....	10	1.00	70	7.00	123	12.30	205	20.50	338	33.80
Age 65 to 74.....	30	1.00	135	4.50	265	8.83	432	14.40	696	23.20
Age 75 plus.....	46	1.00								
Total.....		1.00		5.49		9.91		17.41		23.93
Ex-cigarette smokers only.....				.95		3.48		9.33		8.24

¹ DR, Death rate; MR, Mortality ratio.

SOURCE: U.S. veterans study (app. table A (40)).

The mortality ratios of the Dorn (49) study can be compared with those of the Canadian veterans study, in table 6:

TABLE 6.—*Lung cancer mortality ratios for Canadian veterans by age, type, and amount of smoking*

	Number of cigarettes/day			
	0	1-9	10-20	21+
Current cigarette smokers only:				
Age 30 to 49.....	1. 00	2. 47	4. 15	4. 08
Age 50 to 69.....	1. 00	10. 71	26. 92	26. 83
Age 70 plus.....	1. 00	12. 15	9. 43	24. 53
Total.....	1. 00	10. 00	16. 41	17. 31
Ex-cigarette smokers only total.....				
	6. 06			

SOURCE: Canadian Pensioners study (8), Table 8.1 and 8.2.

From the data shown in table 2 mortality ratios of 17.47 and 29.84 may be noted for smokers of 40+ cigarettes per day, age 55-69 and 70-84, respectively. The Dorn (49) study (see table 5) similarly shows mortality ratios of 33.80 and 23.20 for smokers of 40+ cigarettes per day, age 55-64 and 65-74, respectively. The Canadian study (see table 6) shows mortality ratios of 26.83 and 24.53 for smokers 50-69 and 70 years of age and older respectively who smoked over 20 cigarettes per day. There is rather close agreement among the three large prospective studies for the general range of mortality ratios observed in heavy smokers. From the data supplied by the Doll and Hill survey of British physicians (28, 29) a mortality ratio of 31.86 can be calculated for all smokers of more than 25 cigarettes per day, as compared to a mortality ratio of approximately 8, for smokers of 1-14 cigarettes per day (see table 8).

There is relatively little risk of lung cancer associated with pipe or cigar smoking, probably because smoke from these sources is rarely inhaled. "Mixed smokers," i.e., smokers of cigarettes, pipes, and/or cigars, have less risk than do smokers of cigarettes only, also suggesting that they may smoke fewer cigarettes or inhale less tobacco smoke than do smokers of cigarettes only (see tables 7 and 8).

TABLE 7.—*Lung cancer mortality ratios by type and amount smoked*

All amounts per day	Current smokers of cigarettes only				Current pipe and/or cigar only	Ex-smokers of cigarettes only
	1-9	10-20	21-30	40+		
12. 14	5. 49	9. 91	17. 41	23. 93	1. 67	5. 00

SOURCE: U.S. veterans study [app. table A (49)].

TABLE 8.—*Lung cancer death rates by type of smoker and amount smoked*

Nonsmokers	All smokers	Cigarette smokers				Given up cigarette smoking	Mixed smokers	Pipe or cigar
		All amounts per day	1-14	15-24	25+			
7	71	120	57	129	223	24	52	43

SOURCE: Study of British physicians [tables 23 and 24 (28)].

TABLE 9.—*Lung cancer death rates for ex-smokers of cigarettes by length of time stopped smoking*

Continuing cigarette smokers	Ex-smokers				Nonsmokers
	Less than 5 years	5-9 years	10-19 years	20+ years	
128	67	49	18	19	7

SOURCE: Study of British Physicians [table 25 (28)].

The preceding studies show appreciably lower mortality ratios and death rates from lung cancer with the cessation of cigarette smoking (see tables 4, 5, 6, 7, 8, 9). This lower risk is evident irrespective of the quantity of cigarettes formerly smoked.

The Doll and Hill study (28) of British physicians is of particular interest in respect to ex-smokers. Over the 10-year period of the study (1951-61) 29 percent of the smokers of cigarettes only, had significantly decreased (one-half pack cigarettes or more) their smoking (including those who stopped) and 5 percent had switched to pipes and/or cigars.

While the overall lung cancer mortality of men over age 25 in England and Wales had increased 22 percent over this 10-year period, that for the physician group decreased 7 percent. Since the total physician group is involved in these figures, we can compare this population group to the entire population of England and Wales where there was no general decrease in amount of smoking. This can be thought of as a controlled cessation experiment and the beneficial

effects of stopping or decreasing the amount of smoking become quite evident.

Wicken (102), in a retrospective study of lung cancer mortality in Northern Ireland during the period 1960-62, reported the following results (Table 10) :

TABLE 10.—*Lung cancer mortality ratios and death rates, by sex, age 35 and over, by type and amount of smoking, Northern Ireland, 1960-62*

	Non-smokers	Cigarette smokers amount per day			Cigarettes and pipe and cigar	Pipe and cigar only
		1-10	11-22	23+		
Male:						
Mortality ratios.....	1. 00	4. 83	9. 33	21. 2	5. 22	2. 27
Death rates.....	18	87	168	383	94	41
Female:						
Mortality ratios.....	1. 00	2. 27	6. 72	19. 0	-----	-----
Death rates.....	11	25	74	210	-----	-----

SOURCE: Wicken, A. J. (102), Table 17.

Wicken also analyzed the proportion of lung cancer deaths which would have occurred if the lung cancer mortality rates of the least susceptible groups had been applied to the whole population of Northern Ireland, and found that males would have had only 18 percent of the lung cancer mortality if none smoked and that if they lived in truly rural areas they would have only 10 percent of the mortality. Thus, the difference—8 percent—may be attributable to the urban or suburban residence factor, possibly air pollution. If no females smoked, they would have had only 65 percent of the total female lung cancer mortality, and 53 percent if they lived in truly rural areas. Thus, for females, the difference of 12 percentage points might be attributed to the urban environment. The magnitude of these differences depends on the prevalence of lung cancer in the various sub-groups of the particular population studied.

HISTOPATHOLOGY OF LUNG TUMORS

Classification of lung cancer by histologic type was discussed in the Surgeon General's 1964 Report with the conclusion that the squamous, undifferentiated, and oat-cell carcinomas were far more frequently found in smokers than in nonsmokers, while adenocarcinoma was relatively more frequent in nonsmokers, especially women. Changes in the bronchial mucosa resulting from the inhalation of cigarette smoke included loss of cilia, basal cell hyperplasia, and the appearance of atypical cells with irregular hyperchromatic nuclei. These changes, it was concluded, were related to the premalignant process of the de-

velopment of invasive carcinoma. Auerbach (5) has more recently reported on a study of the pathology of the tracheobronchial trees of 339 men who died from causes other than lung cancer and of 63 men who died from lung cancer. Up to 55 cross-sections of the tracheobronchial tissue were studied in each case. The 339 non-lung cancer cases included 65 men who had never smoked cigarettes and 274 men who had smoked in various amount. Figure 3 shows that only 1.3 percent of the slides from those who never smoked regularly have 60 percent or more atypical cells, whereas 76 percent of the slides of those smoking more than two packs a day had 60 percent or more atypical cells. (See figs. 3 and 4).

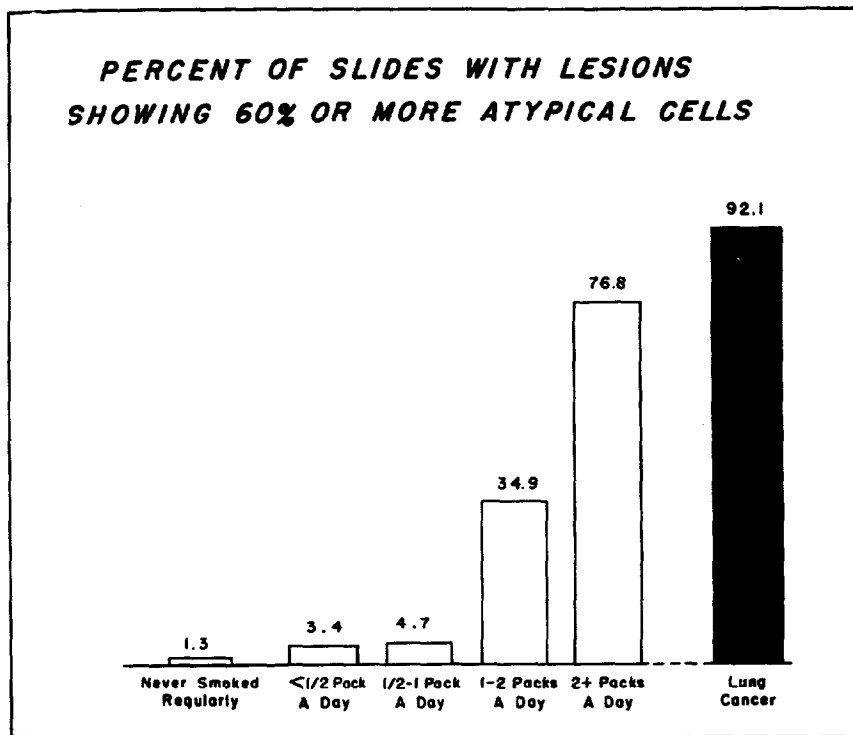


FIGURE 3.—Percent of slides with lesions showing 60 percent or more atypical cells

Source: Auerbach, O., et al. [Table 1(5), updated 1967]

Auerbach (4) has also studied the bronchopulmonary autopsy material from 255 men and three women who died of lung carcinoma of varying histological types, ranging in the spectrum of the WHO classification (103) from the highly differentiated to the undifferentiated squamous cell carcinoma, with others being oat cell, polygonal cell, acinar, and adenocarcinoma. A search for double primaries was made, and by using strict criteria, multiple primary invasive carcinoma was found in 3.5 percent of the autopsies studied. When less

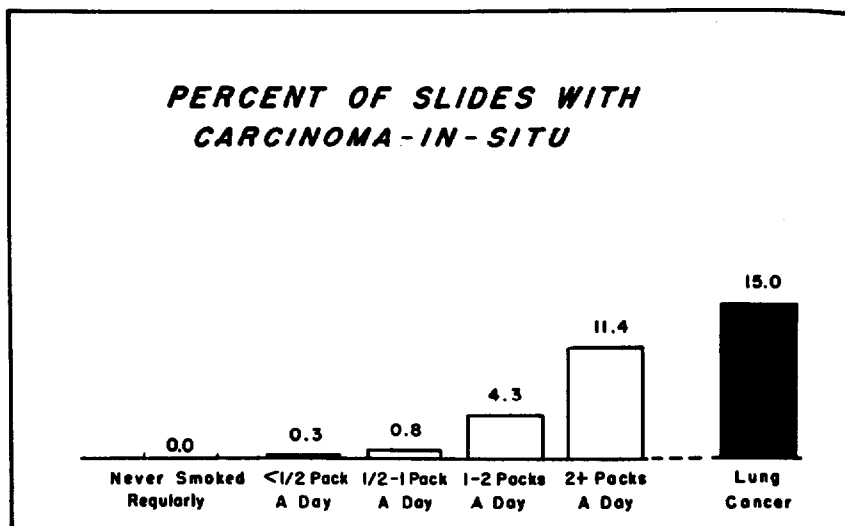


FIGURE 4.—Percent of slides with carcinoma *in situ*.

Source: Auerbach, O., et al. [Table 2(5), updated 1967].

strict criteria were used, but very doubtful cases excluded, up to 12.5 percent double primaries were found. This study suggests that multiple primary bronchial carcinomas in the same patient may be more frequent than previously suspected. Further studies are necessary in this area, since therapeutic implications are also involved.

The differentiation of tumor types as related to smoking habits in various groups with clinically diagnosed lung cancer has again been investigated in several recent studies. In one study (19), of 417 cases of histologically proven lung cancer, 87 percent were smokers. Among the squamous cell cancer cases 89 percent were smokers; among the undifferentiated cell cancer cases 90 percent were smokers, and among those with adenocarcinomas, 60 percent were smokers. A study (99) dealing specifically with alveolar cell cancer of the lung reports that 91 percent of the 180 males in whom this tumor type was diagnosed were smokers and, similarly, that 65 percent of the 85 females with this type tumor were smokers. Another study (104) was made of lung cancer cases in nonsmokers, defined as persons smoking not more than one cigarette a day for 10 years. This study group included eight males and 26 females. Of this group, only four patients had epidermoid carcinoma (two males and two females). Both males had a history of occupational exposure to respiratory irritants. Of the two women, one had an unusual history of carcinoma, including multiple basal cell skin cancers and *in situ* carcinoma of the cervix.

A study (1) was made of 666 histologically proven cases of lung cancer. A smoking history was recorded on 442 of the men in this

series. The chart below takes into account smoking histories as related to three histologic groups: undifferentiated, squamous, and adenocarcinoma (see table 11).

TABLE 11.—*Distribution of lung cancer deaths by cellular type and type of smoking*

Cellular type	Nonsmoker	Pipe smoker	Cigarette smoker
Undifferentiated.....	4	14	124
Squamous.....	6	24	211
Adenocarcinoma.....	2	1	56

SOURCE: Ashley, D. J. B., et al. [(1).Table 4.]

Insufficient information is provided in this study to specify in detail the past smoking histories, but the data suggest that cigarette smoking may be related to adenocarcinoma in some instances.

The preceding studies indicate that squamous, undifferentiated, and oat-cell carcinoma rarely occur in nonsmokers. However, it appears that cigarette smoking may also be associated with alveolar cell carcinoma and glandular carcinoma of the bronchi. This relationship has been previously suspected. In fact as early as 1950 Wynder and Graham (105) demonstrated this relationship. This was also shown in the study by Haenszel (39). Greater standardization and precision of diagnoses are needed to establish how few cases of undifferentiated or squamous carcinoma occur in nonsmokers who have been established to have never smoked appreciable amounts during their lifetimes. If 100 percent accurate smoking histories were obtainable on every case of lung cancer, it is suspected that very few cases of undifferentiated or squamous cancer would be found in persons who had never smoked.

A report (98) on lung cancer in uranium miners noted a frequency of lung cancer, occurring almost entirely in the cigarette-smoking miners, greater than the frequency to be expected in a similar sized cigarette-smoking nonuranium mining population. A recent report (85) on bronchogenic carcinoma in asbestos workers also noted an increased frequency of lung cancer, occurring entirely in the cigarette smoking asbestos workers. This frequency was greater than the frequency to be expected for a similar population of cigarette smokers who were not asbestos workers. These reports suggest that cigarette smoking may interact with certain other environmental exposures to increase the frequency of lung cancer occurrence still further.

Analysis of occupation and other environmental exposures must be performed simultaneously to detect which interactions with smoking seem to be especially dangerous.

EXPERIMENTAL PULMONARY CARCINOGENESIS

Experimental attempts to produce lung cancer involve the administration of tobacco smoke condensates and of carcinogens known to be present in tobacco smoke, either *in vitro* to preparations of cells or *in vivo* in experimental animals. Difficulties are encountered with the viability of tissue cultures and experimental animals when subjected to these various substances. Studies of human tissue from lung cancer patients indicate that abnormalities of the tracheobronchial mucosa, such as loss of cilia, basal cell hyperplasia, squamous metaplasia, and cellular atypism are important in the pathogenesis of human lung cancer caused by smoking. These changes have been experimentally produced in dogs exposed to cigarette smoke through a tracheostomy (2, 79, 80). A large number of dogs is now being studied to determine if lung cancer can be experimentally produced by this technique; if the dogs continue to smoke for a longer time, malignant changes may appear subsequent to the already noted premalignant changes. The squamous metaplasia involved in the premalignant changes may explain why cigarette smoke condensate most readily produces cancer in the squamous epithelium of the skin of laboratory animals.

ADDITIONAL EVIDENCE CONCERNING EXPERIMENTAL CARCINOGENESIS

The inhalation of tobacco smoke by mice was reported to increase the frequency of glandular tumors (37, 41, 63, 70). Syrian hamsters exposed to cigarette smoke developed a small number of tumors in the tracheobronchial epithelium (30, 110). Cigarette smoke condensate has been studied in tissue culture preparations (38), and implantation of cigarette smoke condensate exposed lung tissue subcutaneously has been reported to cause malignant growths (26). Cigarette smoke condensate also causes skin tumors when applied topically (9, 11, 46, 48, 61, 74, 82, 107, 108). This was confirmed by a large-scale study with about 8,000 mice by the Tobacco Industry Research Council of England (22). Repeated injections of cigarette smoke condensate in rats produced sarcomas (32, 82, 83, 84). Since 1963 two studies have reported negative results when cigarette smoke condensate was administered intratracheally to rats and Syrian hamsters (25, 42), respectively.

Bronchoscopic painting of cigarette smoke condensate rapidly causes squamous metaplasia in dogs and may accelerate carcinogenesis (91). Carcinogens, known to be present in tobacco smoke, have been applied to cells in tissue culture with the observation of malignant changes (7) and other effects (21), such as differential growth inhibition of normal but not malignant cells (23). Inhalation (53, 78, 90), intratracheal administration (25, 36, 42, 54, 81), subcutaneous, intraperitoneal and intravenous injection, oral administration, and skin painting of carcinogens have all induced pulmonary tumors (87).

The search continues for an experimental animal system in which the inhalation of tobacco smoke will produce malignant tissue changes closely approximating those observed in human pulmonary cancer. When dealing with passive inhalation of tobacco smoke, however, a problem of the defensive barrier of the nasal passage is introduced. So far, dogs inhaling cigarette smoke through tracheostomies seem to be the most promising system, but there are problems in keeping the experiments going for the length of time necessary for lung cancer to develop. Additional research is needed using cultured lung tissue together with autograft and homograft studies to determine *in vivo* results. Additional insight may thus be gained into *in vivo* systems. It should be noted, however, that it may not be possible ever to achieve histologic identity in pulmonary cancer production, not only because of difficulties in duplication of man's smoking action for reasons of anatomic and physiologic differences, but also because of inherent species' differences in cellular response.

CANCER OF THE BUCCAL CAVITY AND PHARYNX (LIP, MOUTH, THROAT)

The Surgeon General's 1964 Report concluded that the causal relationship of pipe smoking to the development of cancer of the lip appeared to be established. Although there were suggestions of a relationship between cancer of other specific sites of the oral cavity and the several forms of tobacco use, their causal implications could not be stated at that time.

The National Center for Health Statistics (94) reports that during 1964, 28 female and 157 male deaths occurred from cancer of the lip. During the period 1950-64, male mortality from this disease declined about 67 percent. This was partially due to changes in the diagnostic classification but was mainly due to increased early diagnosis and therapy. During the period 1958-64 when the seventh revision of the International Classification of Diseases was in use, total mortality from cancer of the lip remained about the same, but when analyzed by age, substantial decreases occurred in this death rate for each 10-year age group from 55-84 years.

As for cancer of the oral cavity, other than the lip, the total death rate showed no marked variation from 1950-64 (3.1 and 3.3 deaths per 100,000 population, respectively). In 1964, the death rate for cancer of these sites in the male population was about three times the corresponding rate in the female population (5.1 and 1.6 deaths per 100,000 population, respectively).

MORTALITY DATA FROM THE LARGE PROSPECTIVE STUDIES

Hammond (40) has reported data for males having cancer of the buccal cavity or pharynx, as the underlying cause of death, by mortality ratio and age-standardized death rates (table 12).

TABLE 12.—*Buccal cavity and pharyngeal cancer mortality ratios and death rates for male smokers, by type and specified age groups*

	Cigarettes		Pipe and/or cigars
	Males 45-64 years	Males 65-79 years	Males 55-84 years
Mortality ratio.....	9.90	2.93	4.94
Death rates.....	¹ (1) 8	¹ (7) 20	¹ (3) 15

¹ Numbers in parentheses indicate death rates of persons who had never smoked cigarettes regularly.
SOURCE: Hammond, E. C. (40).

The Dorn study (49) also has provided information with relation to amount and type of smoking on males dying from cancer of the buccal cavity and pharynx (table 13):

TABLE 13.—*Buccal cavity and pharyngeal cancer mortality ratios and death rates for U.S. veterans, by age, type, and amount of smoking*

	Current smokers of cigarettes only					Pipe and/or cigars	Cigars only	Pipe only
	Number of cigarettes per day							
	0	1-9	10-20	21-39	40+			
Buccal Cavity:								
Mortality ratio.....	1.00	0.86	2.93	7.34	5.73	3.89	4.11	3.12
Death rates:								
Age 45 to 54.....						28		97
Age 55 to 64.....	2	3	6	12	9	5	3	2
Age 65 to 74.....	4		10	19	9	15	18	11
Age 75 plus.....						12	33	
Pharynx:								
Mortality ratio.....	1.00	7.11	12.81	14.59	19.34	3.06		1.96
Death rates:								
Age 55 to 64.....		9	8	8		2		
Age 65 to 74.....	1	12	22	10	39	4		4

SOURCE: U.S. veterans study (app. table A (49)).

The Canadian pensioners study (8) has not reported separately on deaths from cancer of the buccal cavity and pharynx.

The Doll and Hill studies (28, 29) of British physicians have reported on cancer of the mouth and pharynx, including cancer of the nose (table 14).

TABLE 14.—*Death rates from cancer of upper respiratory tract and digestive system by site and type of smoker*

Site	Non smokers	All smokers	Cigarette smokers	Mixed smokers	Pipe or cigar smokers
Mouth, pharynx, or nose.....	0	6	5	10	4
Larynx or trachea.....	0	6	5	3	10
Esophagus.....	4	10	6	19	8

SOURCE: Study of British physicians, (table 12 (88)).

Data on the relationship between amount of cigarettes smoked and the death rates were also provided (see table 15).

TABLE 15.—*Death rates from cancer of upper respiratory tract and digestive system by site and amount smoked*

Site	Amount of tobacco smoked daily (g.) ¹					
	Non-smoking	All amounts	1-14	15-24	25+	Cessa-tion
Mouth, pharynx, or nose.....	0	7	4	1	21	6
Larynx or trachea.....	0	6	2	2	15	5
Esophagus.....	4	12	8	14	20	2

¹ (g.) = 1 gm. = 1 cigarette per day = $\frac{1}{4}$ oz. tobacco per week.

SOURCE: Study of British physicians (table 13 (88)).

Additional significant information comes from a study (69) of 102 cigarette smokers, all of whom were "cured" of a primary mouth or throat cancer and remained asymptomatic for at least 3 years. Of these patients, 37 stopped smoking while 65 continued. Of the 37 who stopped smoking, only two had a second primary cancer develop in a different site in the buccal-pharyngeal area, whereas 14 of those who continued to smoke developed a second cancer in a different site in the buccal-pharyngeal area.

EXPERIMENTAL STUDIES

In one study (56), pipe smoke condensate was dissolved in sputum and applied behind the ear of mice. Although no ear lesions were observed, two animals developed scirrhous and planocellular cancer, respectively, of the lower jaw, perhaps as a consequence of licking the ears of other mice. In another experiment (37), rats were placed in chambers and exposed to cigarette smoke. Five of 68 surviving rats developed tumors of the buccal mucosa, three of these animals had malignant invasive lesions.

In another setting (27), in which the oral area of mice was painted with cigarette smoke condensate for 15 months, no lesions were noted in the oral cavity. However, a significant increase in lung tumors, lymphosarcoma, leukemia, and reticulosarcoma was observed.

RÉSUMÉ

The Surgeon General's 1964 Report established the causal relationship of pipe smoking with lip cancer, but did not find sufficient evidence for a causal relationship of specific forms of smoking with cancers of other sites in the oral cavity and pharynx. Current information strengthens the association between the various forms of smoking and the general category of cancers of the buccal-pharyngeal area but present information remains inadequate for a judgment of causality. Knowledge of the interaction of smoking and other factors known or suspected as causative agents, when available, could assist in such a judgment.

CANCER OF THE LARYNX

The Surgeon General's 1964 Report concluded: "Evaluation of the evidence leads to the judgment that cigarette smoking is a significant factor in the causation of laryngeal cancer in the male."

The National Center for Health Statistics reports (94) that 2,494 deaths attributed to cancer of the larynx occurred in 1964, as compared with 1,852 deaths in 1950, a 34 percent increase. Almost all these deaths occurred in the male population, with a male-to-female ratio of about 8 to 1. The total death rate in 1964 was 1.3 deaths per 100,000 population, which represented only a slight increase over the death rate of 1.2 noted in 1950. The mortality impact of this disease occurs primarily after middle age, there being a five-fold increase in the death rate for males over 75 years as compared to males under 55 years of age.

The Hammond study (40) reports the following information for laryngeal cancer deaths of males with a history of regular cigarette smoking, in terms of mortality ratios and death rates:

TABLE 16.—*Laryngeal cancer mortality ratios and death rates for male cigarette smokers, by specified age groups*

	Cigarette smokers	
	Age 45-64	Age 65-79
Mortality ratios.....	6. 09	8. 99
Death rates.....	¹ (1) 4	¹ (2) 14

¹ Numbers in parentheses indicate death rates of persons who had never smoked cigarettes regularly.
SOURCE: Hammond, E. C. [table 24 (40)].

The Dorn study (49) of U.S. veterans reports the following laryngeal cancer mortality ratios related to amount of cigarettes smoked, and smoking of pipes and cigars, or cigars only.

TABLE 17.—*Laryngeal cancer mortality ratios and death rates for U.S. veterans, by age, type, and amount of smoking*

	Number of cigarettes per day					Pipe and cigar	Cigar only
	0	1-9	10-20	21-39	40+		
Mortality ratio.....	1	3.27	8.45	13.62	18.85	7.28	10.33
Death rates:							
Age 55 to 64.....	1	-----	4	5	20	4	3
Age 65 to 74.....	-----	7	13	17	-----	12	20
Age 75 to 84.....	13	-----	-----	-----	-----	-----	-----

SOURCE: U.S. Veterans study [app. table A (49)].

The Doll and Hill study reported their data in terms of cancer of the larynx or trachea (see tables 14 and 15) for relationships with type and amounts of tobacco smoking.

The Canadian study did not provide separate data on cancer of the larynx. No additional information has become available, since the Surgeon General's 1964 Report, relating the several forms of smoking, i.e., cigarettes, cigars, and/or pipes, to specific laryngeal cancer sites (intrinsic versus extrinsic larynx).

The study previously referred to (69) which analyzed the development of second sites of cancer after cure of a primary oral cancer, reports that of 37 smokers who stopped smoking, none developed cancer of the larynx but that four of 65 continuing smokers developed cancer of the larynx. Although small numbers are involved, beneficial aspects of smoking cessation are suggested.

RÉSUMÉ

Additional epidemiological evidence supports the previous conclusion that cigarette smoking is a significant factor in the causation of cancer of the larynx.

CANCER OF THE ESOPHAGUS

The Surgeon General's 1964 Report concluded: "The evidence on the tobacco-esophageal cancer relationship supports the belief that an association exists." However, the Committee at that time noted that there was not adequate data on which to base a decision as to whether the relationship was causal.

The National Center for Health Statistics (94) reports that from

1950 to 1964 the mortality from cancer of the esophagus rose about 8 percent in the male population and 9 percent in the female population. In 1964, males had a death rate for esophageal cancer that was 3.7 times higher than the female rate. The greatest relative increases were in the age groups under 65 years, especially the age group 35-44 years.

MORTALITY DATA FROM THE LARGE PROSPECTIVE STUDIES: The Hammond (40) study reports the following death rates and mortality ratios for males in the age groups 45-64 and 65-79 who have a history of smoking regularly:

TABLE 18.—*Esophageal cancer mortality ratios and death rates for male cigarette smokers, by specific age groups*

	Age 45-64	Age 65-79
Mortality ratios.....	4.17	1.74
Death rates.....	¹ (1) 4	¹ (4) 7

¹ Numbers in parentheses indicate death rates of persons who have never smoked regularly.

SOURCE: Hammond, E. C. [table 24 (40)].

The Dorn study (49) reports the following mortality ratios and death rates in relation to number of cigarettes smoked per day plus other forms of smoking:

TABLE 19.—*Esophageal cancer mortality ratios and death rates for U.S. veterans, by age, type, and amount of smoking*

	Number of cigarettes per day					Pipe and cigar	Cigar only	Pipe
	0	1-9	10-20	21-39	40+			
Mortality ratios....	1.00	1.76	4.71	11.50	7.65	4.05	5.33	1.99
Death rates:								
Age 55 to 64....	1	2	5	14	9	5	8	-----
Age 65 to 74....	3	-----	16	25	10	20	23	18
Age 75 to 84....	45	-----	-----	-----	-----	41	-----	72

SOURCE: U.S. Veterans study [app. table A (49)].

The Canadian veterans study did not give separate information about deaths from esophageal cancer.

Autopsy studies of smokers as compared with nonsmokers, specifically observing the pathological changes in esophageal tissue, have been performed by Auerbach (3). A microscopic study was made of 12,598 sections of esophageal autopsy tissue from 1,268 men, who died from causes other than esophageal cancer. The smoking histories were recorded but not known to the person examining the slides. The findings were strikingly similar to the abnormalities generally accepted as

representing premalignant tissue changes in the respiratory tract epithelium. Esophageal epithelial cells with atypical nuclei were found far more frequently in cigarette smokers than in nonsmokers. The term "atypical nuclei" describes nuclei with an irregular distribution of chromatin. Other abnormal changes including giant nuclei may also be present. Basal cell hyperplasia and hyperactive glands also were found more frequently in cigarette smokers than in nonsmokers. An increase in frequency with amount of cigarette smoking was noted for both epithelial cells with atypical nuclei and basal cell hyperplasia. Atypical nuclei in epithelial cells were also more frequently found in ex-cigarette smokers as compared to nonsmokers. Tables 20 and 21 illustrate the frequency of these findings:

TABLE 20.—*Atypical nuclei in basal cells of epithelium of esophagus of males, by smoking habits and age*

Atypical nuclei	Never smoked regularly		Current cigarette		Ex-cigarette		Pipe, cigar		Other	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
A. ALL MEN										
Number men	91		779		181		89		62	
Total sections ¹	787	100.0	6,752	100.0	1,686	100.0	766	100.0	522	100.0
No atypical nuclei.....	733	93.1	167	2.5	770	48.5	53	6.9	195	37.4
Some but <60 percent atypical.....	52	6.6	5,389	79.8	765	48.3	688	89.8	317	60.7
60 percent or more atypical.....	2	0.3	1,196	17.7	51	3.2	25	3.3	10	1.9
B. MEN UNDER AGE 50										
Number men	26		236		28		9		7	
Total sections ¹	223	100.0	2,069	100.0	258	100.0	77	100.0	53	100.0
No atypical nuclei.....	190	85.2	71	3.4	56	21.7	1	1.3	4	7.5
Some but <60 percent atypical.....	33	14.8	1,853	90.0	195	75.6	74	96.1	46	86.8
60 percent or more atypical.....			135	6.6	7	2.7	2	2.6	3	5.7
C. MEN AGED 50-69										
Number men	44		445		109		38		31	
Total sections ¹	379	100.0	3,853	100.0	953	100.0	310	100.0	256	100.0
No atypical nuclei.....	373	98.4	83	2.2	461	48.4	37	11.9	74	28.9
Some but <60 percent atypical.....	4	1.1	2,915	75.6	452	47.4	261	84.2	178	69.5
60 percent or more atypical.....	2	0.5	855	22.2	40	4.2	12	3.9	4	1.6
D. MEN AGED 70 OR OLDER										
Number men	21		98		44		42		24	
Total sections ¹	186	100.0	840	100.0	375	100.0	379	100.0	213	100.0
No atypical nuclei.....	170	91.9	13	1.5	253	67.4	15	4.0	117	54.9
Some but <60 percent atypical.....	15	8.1	621	74.0	118	31.5	353	93.1	93	43.7
60 percent or more atypical.....			206	24.5	4	1.1	11	2.9	3	1.4

¹ Sections with some epithelium present.

SOURCE: Auerbach, O., et al. [table 2(3)].

TABLE 21.—*Atypical nuclei in basal cells of epithelium of esophagus of males, by amount of smoking and age*

Cells with atypical nuclei	Never smoked regularly		Current cigarette smokers					
			<1 Pack		1-2 Packs		2+ Packs	
	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent
A. All ages.....	91		179		413		187	
Total sections ¹	787	100.0	1,544	100.0	3,629	100.0	1,579	100.0
No atypical nuclei.....	733	93.1	89	5.8	39	1.1	39	2.5
Some but <60 percent atypical.....	52	6.6	1,341	88.8	2,957	81.5	1,091	69.1
60 percent or more atypical.....	2	0.3	114	7.4	633	17.4	449	28.4
B. Men under age 50:								
Number men.....	26		49		132		55	
Total sections ¹	223	100.0	433	100.0	1,169	100.0	457	100.0
No atypical nuclei.....	190	85.2	48	11.1	21	1.8	2	0.4
Some but <60 percent atypical.....	33	14.8	282	64.9	1,089	93.2	382	83.6
60 percent or more atypical.....			3	0.7	59	5.0	73	16.0
C. Men aged 50-69:								
Number men.....	44		92		240		113	
Total sections ¹	379	100.0	789	100.0	2,116	100.0	948	100.0
No atypical nuclei.....	373	98.4	30	3.8	18	0.9	35	3.7
Some but <60 percent atypical.....	4	1.1	604	77.9	1,607	75.9	614	64.8
60 percent or more atypical.....	2	0.5	65	8.3	491	23.2	299	31.5
D. Men aged 70 or older:								
Number men.....	21		38		41		19	
Total sections ¹	185	100.0	322	100.0	344	100.0	174	100.0
No atypical nuclei.....	170	91.9	11	3.4			2	1.1
Some but <60 percent atypical.....	15	8.1	265	82.3	261	75.9	95	54.7
60 percent or more atypical.....			46	14.3	83	24.1	77	44.2

¹ Sections with some epithelium present.

SOURCE: Auerbach, O., et al. [table 3(9)].

EXPERIMENTAL STUDIES

Because of the association noted between esophageal cancer and alcohol consumption reported in the Surgeon General's 1964 Report, a study (58) was undertaken to consider the possibility that the carcinogens known to be present in tobacco smoke could penetrate esophageal tissue more readily, if dissolved in aqueous solutions of ethanol. Mice were exposed to several compounds by intraesophageal tubation. Tissues were then removed and studied by fluorescence microscopy. Deeper penetration and a different distribution were found when benzo(a)pyrene was dissolved in aqueous solution of ethanol as compared to benzo(a)pyrene dissolved in olive oil. It was also found that benz(a)anthracene and fluoranthene dissolved in ethanol solution or aqueous caffeine solution could penetrate the epithelium of the esophagus.

RÉSUMÉ

The present evidence strengthens the conclusion that a four-fold to five-fold increased risk of dying from esophageal cancer is associated

with tobacco smoking. Autopsy evidence indicates that smokers have a greater frequency of pathologic changes of the esophageal tissue, some of which are generally considered to be premalignant. It has been demonstrated that known carcinogens such as benzo(a)pyrene and others can penetrate the esophageal tissue when dissolved in aqueous ethanol or caffeine solutions. The present evidence suggests that smoking may be a causal factor in the development of esophageal cancers, but is still insufficient for a firm judgment of causality. More information on alcohol as a confounding variable and/or interactant is vitally needed.

The data on women for the preceding categories of buccal, pharyngeal, laryngeal, and esophageal cancers have not been reported due to the relatively too few cases involved. However, Hammond has pooled these data into one group. Table 22 shows an increased mortality ratio in this overall combined category but the number of deaths is still too small for significant conclusions to be drawn.

TABLE 22.—*Mortality ratios and age-standardized death rates for cancer in women aged 45–64 by site and amount smoked*

Site	Never smoked	Cigarette smoking		Heavier cigarette smoking ¹	
	Death rate	Death rate	Mortality ratio	Death rate	Mortality ratio
Buccal cavity, pharynx, larynx, and esophagus.....	2	3	1.79	6	3.17
Lung ²	7	15	2.17	25	3.63
Pancreas.....	6	11	1.81	16	2.58

¹ Smoked 20 or more cigarettes a day regardless of age, began smoking or smoked 10 or more cigarettes a day, and began smoking before age 25. ² Excluding trachea, pleura.

SOURCE: Hammond, E. C. [table 26 (40)].

Table 22 also shows the dosage effect of smoking on women, for different cancer sites—an increased amount of smoking being reflected in an increased mortality ratio.

CANCER OF THE URINARY BLADDER

The Surgeon General's 1964 Report concluded: "Available data suggest an association between cigarette smoking and urinary bladder cancer in the male but are not sufficient to support judgment on the causal significance of this association."

The National Center for Health Statistics (94) reports that there has been no change in the death rate from cancer of the bladder and other urinary organs during the period 1950–64. For 1964, the male

death rate from this cause was 5.8 deaths per 100,000 population, and the female death rate was 2.6 deaths per 100,000 population.

The mortality data from the large prospective studies are presented below. The Hammond study reports the following mortality ratios and death rates for cancer of the bladder and other urinary tract sites, for males, by history of regular smoking:

TABLE 23.—*Bladder cancer mortality ratios and age-standardized death rates for male cigarette smokers, by specified age groups*

	Cigarette smokers	
	Age 45-64	Age 65-79
Mortality ratios.....	2.00	2.96
Death rates.....	¹ (4)7	(17)50

¹ Numbers in parentheses indicate death rates for persons who have never smoked regularly.

SOURCE: Hammond, E. C. [table 24 (40)].

The Canadian Pensioners study (8) included bladder cancer in the general category of genitourinary cancer.

TABLE 24.—*Genitourinary cancer mortality ratios for Canadian veterans by age and amount smoked*

Mortality ratios	Number of cigarettes smoked per day		
	1-9	10-20	21+
All ages.....	1.33	1.44	1.43
Age 70+.....	1.10	2.24	2.43

SOURCE: Canadian pensioners study [table 8.2 (6)].

The Dorn study of U.S. veterans (49) reports the following mortality ratios and death rates for males by quantity of cigarettes smoked per day and by pipe and/or cigar smoking:

TABLE 25.—*Bladder and other urinary tract cancer mortality ratios and death rates for U.S. veterans, by age, type and amount smoked*

	Number of cigarettes smoked per day					Pipe and/or cigars	Cigars	Pipe
	0	1-9	10-20	21-30	40+			
Mortality ratios.....	1.00	1.10	1.93	3.20	2.52	1.09	0.94	1.20
Death rates:								
Age 45-54.....			13	18				
Age 55-64.....	8	2	12	14	20	14	18	14
Age 65-74.....	22	25	28	96	45	20	9	28
Age 75-84.....	89							

SOURCE: U.S. veterans study [app. table A (49)].

The Doll and Hill survey of British physicians (28) reports the following standardized death rates for cancer of the urinary bladder:

TABLE 26.—*Death rates for cancer of urinary bladder by type of smoking*

Nonsmokers	Type of smoking			
	All smokers	Cigarette smokers	Mixed smokers	Pipe or cigar smokers
17	11	13	12	7

SOURCE: Study of British physicians (table 14 (28)).

TABLE 27.—*Death rates for cancer of urinary bladder by amount smoked*

Amount of tobacco smoked daily (g.) ¹				
1-14	15-24	25+	All amounts	Cessation
10	11	13	12	8

¹ 1 g. = 1 cigarette/day = 1/4 oz. tobacco/week.

SOURCE: Study of British physicians (table 15 (28)).

The Hammond and the Dorn studies report mortality ratios of more than 2.00 in smokers of more than 20 cigarettes per day. The Canadian study reports the same for men over 70 years, who smoke more than 10 cigarettes per day. The Doll and Hill survey is inconsistent with those previously mentioned in that it shows no association between type of smoking or amount smoked and bladder cancer. However, this survey consists of but 38 deaths due to bladder cancer.

Two controlled retrospective studies of bladder cancer patients have been reported since the Surgeon General's 1964 Report. In both studies these patients had a significantly greater percentage of smokers, the majority of whom were cigarette smokers, as compared with controls. The first study (18) reported 94 percent smokers in the patient group and 74 percent in the control group. When analyzed by the amount smoked, the patient group had 80 percent heavy smokers (greater than one pack per day for 30 years) as compared to only 45 percent heavy smokers in the control group. The second study (89) reported 93 percent smokers in the patient group and 84 percent in the control group. However, when compared by the amount smoked, there was a much larger difference between the two groups; there being 86 percent of the patient group with a high "smoking index" (amount smoked × duration of smoking) as compared to only 66 percent in the control group. The latter study also reported a greater frequency of inhalation and "cigarette only" smoking in the patient versus controls groups.

AUTOPSY STUDIES

There have been no reported studies analyzing changes in the bladder tissue of smokers compared with nonsmokers. Studies of this type would be helpful to determine if smoking is associated with pathologic changes commonly thought to be premalignant in other types of tissue.

EXPERIMENTAL CARCINOGENESIS

Cigarette smoke condensate as well as several tobacco smoke constituents were implanted with cholesterol directly into the bladder of mice (16). Only hydroquinone produced a significant number of bladder tumors.

METABOLIC STUDIES OF ENDOGENOUS CARCINOGENIC SUBSTANCES IN MAN

Certain ortho-aminophenols and aryl hydroxylamines are known to be carcinogenic (15). Three normal intermediate metabolites of tryptophan are ortho-aminophenols (3-hydroxyanthranilic acid, 3-hydroxy-2-amino-acetophenone, 3-hydroxykynurenine) and are known to induce cancer when placed in the bladder of mice (15).

Kerr, et al. (51, 52), performed metabolic studies on six men, three smokers and three nonsmokers. He found that the three nonsmokers had substantially increased urinary excretion values of 3-hydroxyanthranilic acid and 3-hydroxykynurenine, after having smoked for 5 weeks, with a concomitant decrease in the excretion of N⁷-methylnicotinamide, a normal end product of tryptophan metabolism. After having stopped smoking for 5 weeks, the three smokers showed decreased urinary excretion of these same intermediate metabolites and an increase in N⁷-methylnicotinamide excretion.

The carcinogenic metabolites increased an average of 50 percent while the normal end metabolite decreased an average of 34 percent in response to cigarette smoking. A reversal was noted after the men stopped smoking. These studies suggest that cigarette smoking changes the normal metabolic pattern of tryptophan, leading to the accumulation of carcinogenic metabolites in the urine. Further studies are needed to confirm these findings.

Another study, designed to detect abnormalities of tryptophan (6) in patients with various neoplastic or nonneoplastic conditions of the urinary tract, showed that 29 of 201 bladder cancer patients had both kynurenine and 3-hydroxykynurenine, in contrast to eight of 167 patients with other urinary tract diseases, neoplastic and nonneoplastic. However, more renal cancer patients had 3-hydroxyanthranilic acid than bladder cancer patients. This study did not include data concerning current smoking habits of the patients studied.

RÉSUMÉ

The additional epidemiological, clinical, and experimental data strengthen the association between cigarette smoking and cancer of the urinary bladder, but are still insufficient to infer that the relationship is causal.

CANCER OF THE STOMACH

The Surgeon General's 1964 Report stated that no relationship has been established between tobacco use and stomach cancer. No new evidence refutes this statement.

Epidemiological evidence does not show a significant relationship between smoking and stomach cancer. The overall mortality ratios, although greater than for nonsmokers, are smaller than for any other disease related to smoking. There is also no gradient with the amount of tobacco smoked.

TABLE 28.—*Male mortality ratios and death rates for cancer of stomach by specified age groups*

	Age 45-64	Age 65-79
Mortality ratios.....	1.42	1.26
Death rates.....	¹ (11) 16	(57) 72

¹ Numbers in parentheses indicate death rates of persons who had never smoked cigarettes regularly.

SOURCE: Hammond, E. C. [table 24 (40)].

TABLE 29.—*Mortality ratios and death rates for cancer of stomach by age, type, and amount smoked, in U.S. veterans*

	Cigarettes/day					Pipe and/or cigars	Cigar	Pipe
	0	1-9	10-20	21-39	40+			
Mortality ratio (total).....	1.00	2.17	1.61	1.35	1.87	1.21	1.20	1.40
Death rate:								
Age 45 to 54.....	10		7					
Age 55 to 64.....	13	27	21	24	53	15	9	21
Age 65 to 74.....	28	68	48	58	46	40	46	57
Age 75 to 84.....	87					114	212	

SOURCE: U.S. Veterans study [app. table A (49)].

TABLE 30.—*Death rates for cancer of stomach by type and amount smoked, in British physicians*

Non-smokers	All smokers	Cigarette smokers	Amount of tobacco daily (g.) ¹				Given up smoking	Mixed	Pipe or cigar
			1-14	15-24	25+	All amounts			
27	25	30	28	28	26	28	18	14	30

¹ 1 g. = 1 cigarette per day = $\frac{1}{4}$ oz. tobacco per week.

SOURCE: Study of British physicians (tables 14 and 15 (23)).

RÉSUMÉ

Although cigarette smokers appear to have slightly higher death rates from cancer of the stomach, the differences are small and do not bear any consistent relationship with amount smoked.

CANCER OF THE PANCREAS

The Surgeon General's 1964 Report did not report on cancer of the pancreas.

The more recent epidemiologic evidence shows an increase in the death rates and mortality ratios for pancreatic cancer among male cigarette smokers (40, 49). Comparably elevated ratios are noted for females but not to the extent noted for males (40) (see tables 22, 31, 32, 33). Both the U.S. veterans study (49) and the Canadian pensioners study (8) reveal a gradient of mortality risk increasing with the amount of cigarettes smoked. Data are insufficient to draw any conclusions for pipe and/or cigar smokers.

TABLE 31.—*Mortality ratios and death rates for cancer of pancreas by sex and specific age groups in cigarette smokers*

	Age 45-64		Age 65-70	
	Female	Male	Female	Male
Mortality ratio.....	1.81	2.69	¹ 1.41	2.17
Death rate.....	² (6) 11	² (7) 19	² (32) 45	² (31) 66

¹ Computed from app. table 19.

² Numbers in parentheses indicate death rates of persons who had never smoked cigarettes regularly.

SOURCE: Hammond, E. C. (tables 24, 26, and app. table 19 (40)).

TABLE 32.—*Mortality ratios and death rates for cancer of pancreas by age, type, and amount smoked, in U.S. veterans*

	Cigarettes/day					Pipe and/or cigars	Cigar	Pipe
	0	1-9	10-20	21-39	40+			
Mortality ratio (total).....	1. 00	. 87	1. 93	2. 18	1. 87	1. 13	1. 52	. 74
Death rate:								
Age 45 to 54.....			9	21		26		
Age 55 to 64.....	13	15	24	26	21	19	21	22
Age 65 to 74.....	29	29	50	56	27	38	58	19
Age 75 to 84.....	109					32	33	68

SOURCE: U.S. veterans study [app. table A (4)].

TABLE 33.—*Male mortality ratios for cancer of pancreas of current cigarette smokers by amount smoked*

	Cigarettes/day			
	0	1-9	10-20	21+
Mortality ratio.....	1. 00	1. 40	1. 96	2. 37

SOURCE: Canadian pensioners study [table 8.2 (8)].

RÉSUMÉ

An association between cigarette smoking and pancreatic cancer is implied, but in the absence of data on other possible causal factors, confounding variables and interactants, the significance of this association is not clear.

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CHAPTER 4

Other Conditions and Areas of Research

CONTENTS

	Page
Smoking and Peptic Ulcer.....	181
Smoking and Disturbances of Vision.....	183
Smoking and Cirrhosis of the Liver.....	184
Effects of Smoking During Pregnancy.....	185
Smoking and Accidents.....	187
Psychosocial Aspects of Smoking.....	188
References.....	193

SMOKING AND PEPTIC ULCER

Since the publication of the Surgeon General's 1964 Report, three of the continuing prospective mortality * studies (2, 3, 6, 7) have provided additional information which confirms the association between cigarette smoking and mortality from peptic ulcer, especially gastric ulcer. The mortality ratios increase with increases in amounts smoked. The tables presented below illustrate the relationships involved. Although Hammond's (6) study contained a large number of females, insufficient deaths from peptic ulcer have occurred in cigarette smoking females to provide statistically reliable data. A trend is observable among cigar and/or pipe smokers with regard to increased mortality from gastric ulcer, but the number of deaths is too small for significant conclusions to be drawn.

TABLE 1.—*Death rates and mortality ratios for gastric and duodenal ulcers by specific age groups of male cigarette smokers*

Site	Age 45-64		Age 65-79	
	Death rate	Mortality ratios	Death rate	Mortality ratios
Gastric ulcer.....	¹ (2) 7	2.95	(7) 26	4.06
Duodenal ulcer.....	(3) 7	2.86	(21) 31	1.50

¹ Number in parentheses indicates death rate for persons who never smoked regularly.

SOURCE: Hammond, E. C. [table 24(6)].

TABLE 2.—*Male death rates and mortality ratios for gastric and duodenal ulcers by specific age groups for current and ex-smokers of cigarettes only*

Site	Current cigarette smokers only				Ex-cigarette smokers only
	Death rate			Mortality ratio (total)	Mortality ratio (total)
	55-64	65-74	75-84		
Gastric ulcer.....	¹ (2) 7	(5) 17	(—) 26	4.13	2.74
Duodenal ulcer.....	(4) 8	(10) 29	(37) 122	2.98	2.13

¹ Number in parentheses indicates death rate for persons who have never smoked.

SOURCE: U.S. veterans study [app. table A (7)].

* All death rates throughout this chapter are per 100,000 population, unless otherwise indicated.

TABLE 3.—*Peptic ulcer death rates by type and amount smoked, in males*¹

Nonsmokers	All smokers	Cigarette smokers				Given up cigarette smoking	Mixed smokers	Pipe or cigar
		All amounts	1-14	15-24	25+			
0	13	13	2	18	19	12	12	10

¹ Includes gastric and/or duodenal ulcers.

Source: Study of British physicians (tables 23 and 24 (#)).

A recent survey (13), based on a national sample of 42,000 household interviews, shows that the prevalence of peptic ulcer is almost 100 percent greater in male cigarette smokers and over 50 percent higher in females who smoke cigarettes as compared to those males and females who had never smoked. Hammond's data (5) shows twice the number of cigarette smokers reporting the occurrence of peptic ulcer over a 2-year follow-up period as contrasted to nonsmokers. This also increases with increases in the amount smoked.

Several small retrospective clinical studies (4, 8, 12) have shown significantly more smokers and less nonsmokers in their peptic ulcer patients as compared to control groups. Doll (1) reviewed various prospective studies on gastric ulcer therapy regimes, such as: diet—bland, normal, high and low fat; milk drips with alkali; drugs; and advice to stop smoking. The best results were obtained in patients who stopped or cut down on their smoking habits. The Surgeon General's 1964 Report (14) points out the conflicting literature concerning the effects of smoking on gastric secretion and motility. Lee (10), in a small series of peptic ulcer patients and controls, showed that after smoking, 74 percent of patients and 58 percent of controls had a significant rise in free gastric acidity. Those subjects with initially normal or hyperacidity had the greatest response, whereas, of those with initial hypoacidity only 28 percent had an increase in gastric acidity. Five of nine controls, smoking a non-nicotine cigarette preparation, also had a rise in gastric acidity, perhaps due to factors in smoke other than nicotine or to oral stimulation.

RÉSUMÉ

Cigarette smoking is shown to be associated with peptic ulcer. This relationship is greater for gastric than duodenal ulcer and is proportional to the amount smoked. The etiology of the peptic ulcer diathesis is still unknown. Smoking is a definite risk factor in peptic ulcer mortality. It may also be a factor in the delay in healing of a gastric ulcer. More research is needed on the physiological effect of smoking on the gastrointestinal tract.

SMOKING AND DISTURBANCES OF VISION

TOBACCO AMBLYOPIA

Recent evidence points to the tobacco and/or alcohol amblyopias as being manifestations of nutritional amblyopia (4, 7, 8, 17, 25, 26). Various deficiencies in factors of the vitamin B complex have been implicated (4, 6, 7, 10, 17, 25, 26).

A new theory that chronic low vitamin B₁₂ levels potentiate the toxic effects of cyanide in tobacco has recently been expounded (8, 10, 22, 23).

The anatomical lesion in amblyopia seems to be a demyelination of the optic pathways, particularly in the papillomacular bundle (10, 17, 25).

In view of the fact that cyanide is neurotoxic, more research is needed in this area to further elucidate its association with this disease entity.

OTHER DISEASES

Several studies have hypothesized that Leber's optic atrophy, which also is attributed to a demyelination process in optic pathways, may be associated with a defect in cyanide detoxification, which is aggravated by the cyanide in tobacco smoke (1, 27).

VISUAL ACUITY

The Surgeon General's 1964 Report, and others, cite evidence of increased levels of carboxyhemoglobin in smokers (20, 24), due to the carbon monoxide content in tobacco smoke. It has been suggested that a decrease in nighttime visual discrimination in smokers is related to this increase in carboxyhemoglobin levels (9, 15, 16, 19). It may also possibly be due to the relative anoxia produced by the carbon monoxide inhalation from tobacco smoke. A value of only 5 percent carboxyhemoglobin saturation, not uncommon in smokers, creates a physiological state of anoxia equivalent to being at an elevation of 8,000 feet, with an arterial O₂ saturation of only 91 percent (15, 16).

RÉSUMÉ

It is suggested that tobacco amblyopia is but a manifestation of nutritional amblyopia, which is aggravated by tobacco smoking. More research is needed on the toxicity of tobacco smoke, with special concern for the cyanide component. Experiments have shown a visual discrimination deficit, possibly related to the carbon monoxide content of tobacco smoke. Further work is needed in this area in order to ascertain any clinical consequences.

SMOKING AND CIRRHOSIS OF THE LIVER

Increased mortality of smokers from cirrhosis of the liver is found in the prospective studies. This has generally been thought to be largely secondary to an association between smoking and heavy alcohol consumption. Published data are inadequate to test this interpretation.

The three prospective studies (1, 2, 3, 4) all show increased death rates and mortality ratios from cirrhosis of the liver in cigarette smokers.

TABLE 1.—*Mortality ratios and death rates for liver cirrhosis by sex and specific age groups*

	45-64		65-79	
	Female	Male	Female	Male
Mortality ratio.....	2.16	2.06	¹ 1.40	1.97
Death rate.....	² (5)10	² (9)19	(10)14	(16)31

¹ Calculated from app. table 19 (3).

² Numbers in parentheses indicate death rates for persons who have never smoked regularly.

SOURCE: Hammond, E. C. [tables 24, 26, and app. table 19 (3)].

TABLE 2.—*Male mortality ratios and death rates for liver cirrhosis by age and amount smoked, in U.S. veterans*

	Current smokers of cigarettes only				
	0	1-9	10-20	21-39	40+
Mortality ratio (total).....	1.00	2.72	3.15	3.61	5.50
Death rate:					
Age 45 to 54.....	9	-----	7	7	162
Age 55 to 64.....	15	12	35	44	46
Age 65 to 74.....	16	74	57	57	87
Age 75 to 84.....	53	-----	-----	-----	-----

SOURCE: U.S. veterans study [app. table A (4)].

Doll and Hill present their data with respect to cirrhosis of the liver and alcoholism combined. See table 3.

TABLE 3.—*Male death rates for liver cirrhosis by type and amount smoked, in British physicians*

	Non-smokers	All smokers	Cigarette smokers	Number of cigarettes				Given up smoking	Mixed smokers	Pipe or cigar
				1-14	15-24	25+	All amounts			
Cirrhosis of liver and alcoholism.....	0	11	12	5	8	43	15	3	11	5

SOURCE: Study of British physicians, [tables 21 and 22 (1)].

The Surgeon General's 1964 Report points out the association between heavy smoking and excessive alcohol intake. In view of the fact that "The increased death rate from cirrhosis among smokers may reflect the consumption of alcohol and associated nutritional deficiencies rather than the effect of cigarette smoking" (5), further research is needed to elucidate the association between smoking and cirrhosis of the liver.

EFFECTS OF SMOKING DURING PREGNANCY

The current new literature on pregnancy and smoking supports the Surgeon General's findings that there are a greater number of "low birth weight" babies and premature babies as defined by weight alone (2,500 g.) in those women who smoke during their pregnancy (6, 9, 18, 20, 21, 24-26, 28, 30-32, 36). Furthermore, this decreased weight has been shown to be consistent in each trimester (28, 31, 32, 34, 36) and is proportional to the amount smoked during pregnancy (5, 24-26, 30-32, 34, 36).

There are many factors which affect the outcome of pregnancy. These include constitutional, pathobiological and psychological factors. Multiple-regression analyses of these various factors have shown smoking to be a significant negative independent variable with respect to birth weight (1, 5, 27).

Smoking has been linked to increased incidence of abortions and/or stillbirths (6, 25, 26, 28, 30, 36), premature rupture of membranes (30-32) and decreased male/female birth ratios (11, 25, 26); however, other studies do not support these findings (7, 9, 24, 30-32).

The significance of low birth weight and prematurity in regard to increased fetal and infant mortality, has not been clearly demonstrated. Most studies show no increased mortality (9, 31, 32). However, Yerushalmy (34) and Underwood (32), point out that although the overall mortality is the same between infants of smoking versus nonsmoking mothers, premature babies (as defined by birth weight of less than 2,500 g.) of smoking mothers have decreased mortality. Other studies show a slight but significant increase in fetal mortality for mothers who smoke (6, 8). MacMahon (19) shows that rather than increasing the proportion of low birth weight babies, smoking actually causes a shift to the left in the entire weight distribution (fig. 1).

Jansson (15) in his study states: "Thus, in the absence of other complications, smoking mothers seem to make a proportionally greater contribution to infants in the weight group just below 2,500 g. where the prognosis is better."

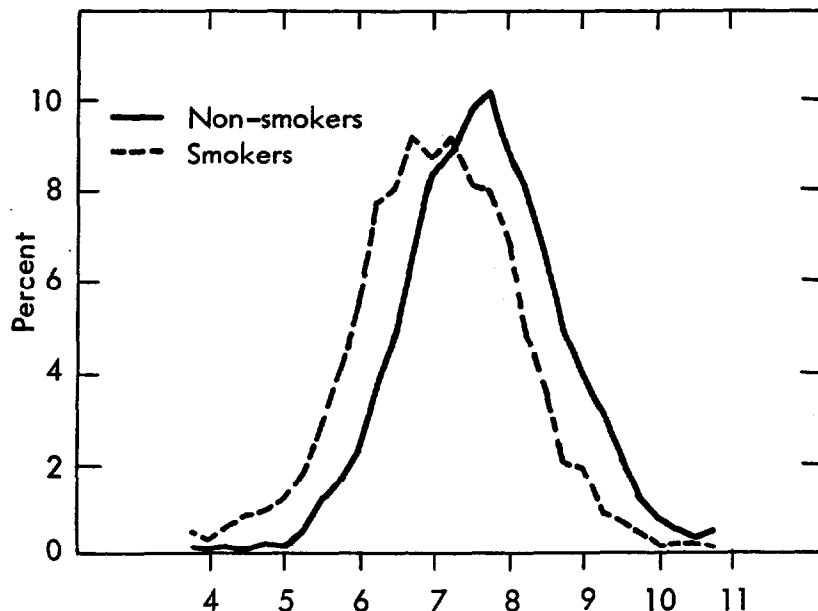


FIGURE 1.—Percentage distribution by birth weight¹ of infants of mothers who did not smoke during pregnancy and of those who smoked one pack or more per day.

Source: MacMahon, B., et al. [fig. 1 (19)].

Steele (29) suggests that smoking is associated with sudden unexpected deaths in infancy. The relationship of smoking in mothers to increased fetal morbidity, either perinatally or after long-term follow-up, has not been adequately probed and is a major area for future research.

Some studies show a relationship between smoking and decreased gestational age (6, 8, 32); others do not (1, 27).

Gestational age probably is a better indicator of fetal prematurity than birth weight. Therefore, it may better reflect perinatal risk. Yet even in the studies showing a correlation to smoking, this relationship is less marked than that to birth weight (6, 8, 24, 32). This may be due to the relative difficulty in determining the last menstrual period accurately and therefore the true gestational age.

The mechanisms by which smoking affects pregnancy have not been elucidated. Events influencing decreased fetal birth weight have been attributed to several factors:

1. Placental vasoconstriction due to nicotine. No direct evidence of this exists at the present time. The effects of smoking on uterine blood flow are being conducted in animal experimentation (2).

¹ Birth weight (scale in pounds; intervals of 4 ozs.)

2. Increased carbon monoxide in cord blood (12).
3. Decreased carbonic anhydrase activity due to increase in cord carbon monoxide (20).
4. A postulated direct effect on the fetus of some toxic agent in cigarette smoke.
5. Decreased caloric intake due to decrease in appetite of smokers (10). Several studies have shown that there is no difference in weight gain during pregnancy between smokers and nonsmokers (28, 30, 36). Since smoking in general, does decrease appetite, it might be well to consider a difference in the type and/or distribution of caloric intake between smokers and nonsmokers.

Kumar (17) has shown an increase in human uterine activity after smoking, both in frequency and magnitude of contractions. However, these findings were not observable in every patient. There was no significant effect of nicotine on myometrial strips *in vitro* from pregnant human uteri.

King and Becker (4, 16) have done experimental work with nicotine on pregnant rats. High concentrations of nicotine had greater toxic effects on pregnant rats than controls. The offspring were lighter in weight and survived less well than controls.

RÉSUMÉ

Clearly, more research is needed to elucidate the significance of the relationship of smoking in pregnancy and low birth weight. Additional long-range morbidity studies are needed, as well as studies on the effect of smoking on uterine activity and placental blood flow.

Smoking does have an effect on the outcome of pregnancy. However, it is not known whether this effect is deleterious or not.

Until such evidence is presented so as to clearly define the role of smoking in pregnancy, it is more prudent at this time to advise pregnant women to stop or decrease their cigarette-smoking practices.

SMOKING AND ACCIDENTS

The most obvious contribution of smoking to accidents is as a cause of fires. Estimates of the proportion of fire loss due to "smoking and matches" (includes fires attributed to careless smoking and the careless use of matches and lighters by smokers; does not include misuse of matches by children) vary from 19 percent to 25 percent. The

National Fire Protection Association gives "smoking and matches" as a reported cause of fire in various buildings for 1965 as follows (3) :

	<i>Percent</i>
Apartments	26
Boarding and rooming houses.....	30
Dormitories, etc.....	24
Dwellings (1- and 2-family).....	19
Hospitals	21
Hotels, seasonal.....	24
Hotels, year round.....	35
Motels.....	20
Nursing	25

In 1965 there were 163,900 fires linked to smoking or the matches used in smoking with a concomitant property loss of \$80,400,000—in 1964, there were 159,400 fires and a property loss of \$79,500,000 (5). The statistics on the number of deaths attributed to those fires are not available, but it is estimated that 1,800 people per year will die due to fires caused by smoking and matches (7).

Smoking has been shown to cause decreased visual discrimination especially under conditions of low illumination (4). This could have serious implications with respect to night-time driving.

Several studies (1, 2, 6) have indicated an association between smoking and traffic and industrial accidents, but the evidence is insufficient at this time to draw any significant conclusions. More research is needed in this area.

PSYCHOSOCIAL ASPECTS OF SMOKING

There has been a sharp increase in the attention devoted to behavioral research since the Surgeon General's 1964 Report. A number of new concepts have been developed and more sophisticated multivariate approaches are being used. However, because of the recency of these studies, very little in the way of findings has been published on which firm conclusions may be based.

One of the byproducts of the Surgeon General's 1964 Report has been its stimulation of more research in all areas of smoking, including the psychosocial. Much research will soon be completed but has not yet been reported in the literature.

Three behavioral science conferences have been held since the Surgeon General's 1964 Report. The content of these conferences are either in print (9) or will shortly be published (11, 21). These conferences dealt with many different studies and research findings, theories, methodological criticisms, and discussions on a number of important issues. Among the primary purposes was the development and speeding up of communications among those doing work in the field, pre-

venting duplication and wasted effort, developing better measuring instruments, and providing assistance in conceptualizing new theoretical models or further developing approaches already proposed.

Much prior research in the psychosocial aspects related to smoking, while yielding valuable data and suggestive theory, has been concerned largely with discrete variables or attributes and has looked for gross differences between smokers and nonsmokers. Since it is unlikely that such research will discover that either group possesses an attribute that is unique to it other than the behavior of smoking, the ability of any single attribute to differentiate between these two populations is bound to be limited. It is because of this that a number of investigators have turned toward trying to distinguish subgroups of smokers, as well as toward developing more unifying concepts. These efforts are part of the attempt to obtain greater insight into the dynamics of smoking and develop more powerful predictive instruments.

One area that shows conceptual and methodological maturation is that of the study of smoking and personality. Much prior research studied smoking in relation to such concepts as extroversion, introversion, neuroticism, emotional stability, orality, femininity, masculinity, hypochondriasis, psychosomatic symptoms, risk taking and chance orientation, psychopathic tendencies, achievement needs, social approval, relationships to authority, independence, aggression, and the like.

At the 1966 behavior research conference, it was pointed out that a better understanding of the total personality structure must be achieved in order to increase understanding of some of the psychological correlates of smoking. Factor and hierarchical models have much to contribute to this approach (1). At the 1967 conference this and other points pertinent to personality research related to smoking were discussed, and a reminder of the utility of multivariate techniques was repeated (20). Toward this end these investigators are now studying university students, seeking factors in the realm of personality integration such as experience of control, scope of awareness, reality contact, self-insight, temporal perspective, independence, anxiety, and the like. After these factors have been identified they can be used as independent variables in testing hypotheses suggested by other developments, such as the recently developed typology of smokers, illustrating the potential yield from a cross-fertilization of unifying concepts.

Theories which emphasize the role of anxiety in the development of personality and in the understanding of personality dynamics (7) provide a unifying frame of reference which, when combined with an understanding of the gratifications derived from smoking, may lead to useful explanations and investigations into smoking behavior. They may also provide some cohesiveness to research on such concepts as

guilt, self-punishment, need to fail, and risk-taking behavior as they relate to the initiation, continuation, or inability to discontinue smoking. Concepts from depth psychology, and ego psychology in particular may additionally illuminate the source and function of some of the apparent inconsistencies among attitudes, beliefs, and behavior noted by various investigators beyond that provided by dissonance theory (2).

Another area showing some growth is represented by attempt to distinguish between the different levels of dosage to which smokers expose themselves beyond that indicated by the average number of cigarettes smoked daily. More sophisticated dosage measurements (18) obviously have application in epidemiological research. They may also prove useful in psychosocial research. There is the possibility that an interplay exists between the degree and kind of exposure, physiological and psychological processes, and the dynamics, mechanisms, or degree of difficulty involved in achieving long-term cessation of smoking.

Another conceptual development was contained in the proposal, reported at the first of the national behavioral conferences (16) and later refined (15), of a new way to define smokers—in terms of the smoker's use of cigarettes to help manage affect, i.e., emotions. From the types of smoking identified (habitual smoking, smoking to increase positive affect, to reduce negative affect, and psychologically addictive smoking) and from a theoretical discussion of the dynamics involved in their formation, possibilities exist for the development, testing, and application of theories and techniques for producing cessation either in a clinic or a natural setting. By identifying differences between smokers in the psychological use of cigarettes, the typology makes it possible to develop theories and techniques to reinforce behavior change and to expand knowledge of the dynamics of smoking behavior.

These concepts are undergoing empirical identification and verification at both the national level and in a variety of clinical settings studying behavior change.

In one study (13), for example, which compared three methods of aid to people who were trying to give up smoking, efforts were made to assess the subjects' progress, the nature of the change process, and the social-psychological factors which influence the ability to give up smoking and resist resuming. The investigators are analyzing their data from the conceptual base of smoking types as well as from other points of view in an examination of cessation processes.

The smoking typology is also being applied in an analysis of a survey of adults' and adolescents' smoking habits and attitudes in the United Kingdom (10). At the recent 1967 behavioral conference results were presented showing the relation between these smoker types and nervous irritation and relaxation smoking scales, wishing and trying to give up smoking, and addiction indicators for both adolescents and adults.

There were other kinds of analyses described in this research which provide the stimulus for further development and testing of theory.

In this country, a parallel set of surveys has been going on which utilized many questions from the above-mentioned survey just as that survey also borrowed from it. Cross-cultural comparisons are thus possible.

The national surveys of adult smoking behavior, beliefs, and attitudes in this country stimulated, and were also based upon, an organizing framework which discussed some dimensions of a model for behavior change (6). This framework incorporated the concepts related to the typology of smokers previously mentioned and also leaned heavily on a behavior model developed originally to provide a theoretical base underlying participation in a mass X-ray screening program (3, 4, 12). Four dimensions of the framework are discussed and postulated as being essential in considering whether smoking behavior change will or will not take place. They are: The motivations for change (e.g., the exemplar role, economics, esthetics, mastery, and others beside the health threat); the perception of the threat (e.g., the awareness of the threat, the acceptance of the importance of the threat, the personal relevance of the threat, and beliefs about the susceptibility of the threat to intervention); the reasons for smoking in terms of affect management, and the potential development and use of alternative psychological mechanisms; and factors supporting or inhibiting continuing reinforcement (e.g., the role of social forces, interpersonal influences, the mass media, the behavior and attitudes of certain key groups, and the general level of acceptability of the behavior).

Backed by the longitudinal data at the national level and subject to multivariate analysis, this conceptual framework can potentially be developed to the point whereby the parts may be related quantitatively and qualitatively to each other and thus afford a more dynamic interpretation of the behavior change under consideration. The possibility also exists for the development of an instrument for the prediction of change, as well as an opportunity for the verification of some prospective findings reported earlier (14). These constructs have also since been extended to considerations of the process of either taking up smoking or remaining a nonsmoker (5).

In another area of investigation, one project (19) is concerned not so much with individual differences but with cultural differences in values, attitudes, and behavior related to smoking among various ethnic groups in the Southwest and has as its main assumption the probable existence of a common core of psychosocial factors operating to produce different motivation patterns among young people socialized in a particular cultural environment.

Another kind of research—that of the controlled experiment manipulating one variable at a time with a number of small samples—

has advantages which were discussed at the 1967 behavior research conference (8). The use of such laboratory methods and controls has been shown to be particularly useful in communications research, including the study of factors that affect a person's acceptance and use of health information. More systematic efforts are needed which will relate the content of the message, the form of the message, the kind of medium used, and the characteristics of the communicator to changes in smoking behavior which are also related to the psychosocial nature of the target audience. In particular, emotion-provoking communications need to be studied in relation to various factors that are known to maintain actions, such as public commitment and conformity to group norms.

As in the case with epidemiological investigations, however, it is probable that more prospective research studies combining social-psychological, sociological, and anthropological concepts must be carried out before a better understanding of smoking behavior initiation (or non-initiation), continuation, or change can be achieved.

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PREGNANCY

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