

1. INTRODUCTION AND SUMMARY.

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Introduction

In the 15 years which have elapsed since the Report of the Advisory Committee on Smoking and Health to the Surgeon General of the U.S. Public Health Service (15), there has been an increasing number of scientific studies on the relationship between tobacco consumption and health. Where the 1964 Committee had access to some 6,000 articles in the world literature on smoking and health, there are now more than 30,000 such articles. In fact, no sound epidemiologic study of chronic disease today would omit from its design a history of tobacco use as a significant factor. It is on this greatly expanded source of data that this current review and re-evaluation of the evidence on the hazard of smoking to human health is based.

For historical perspective, it should be remembered that concern over the effect of tobacco on health did not begin with the Report to the Surgeon General, although that evaluation was the first American review and judgmental analysis of the tobacco hazard for all aspects of human mortality, morbidity, and specific diseases other than lung cancer. Indeed, almost from the moment of its introduction into Europe in 1558, the *Nicotiana tabacum* prompted serious concern over the effects which uses of this leaf had on human health. In less than 60 years, tobacco had become a staple agricultural commodity in Virginia and its principal currency. The "tobacco culture" expanded rapidly both societally and agronomically in America; in Europe, in the 17th Century, Simonis Paulli published his treatise "On the Abuse of Tobacco" (6).

Although the growth of tobacco use has been extensively documented, reliable data on its use within the total U.S. population did not become available until 1880 (8). Since then, per capita tobacco consumption has increased almost three-fold, with dramatic changes in its forms of use. Prior to World War I, tobacco chewing was the principal use in the United States, but the 1920's saw cigarette consumption, particularly of prefabricated cigarettes, increase astronomically as use of chewing and other smoking tobacco declined. A cigarette consumption plateau in the 1930's was followed by a sharp increase during World War II, when widespread adoption of the cigarette habit by women was added to large-scale consumption by American troops. These changes in overall consumption and forms of tobacco use had marked influences on mortality and disease patterns.

Concern over the effects of tobacco use on health increased over the years, but it was not until the 20th century that systematic scientific studies of the problem were launched. Clinical impressions and suspicions had been recorded and some had persisted for decades and centuries before appropriate tools for scientific investigation were developed. For example, the relationship between cancer of the lip and tobacco use was noted by Holland early in the 18th century (5) and Soemmerring made the same observation in 1795 (13). Not until 1920.

however, was the first systematic approach to that association made (1). In 1900, statisticians began to note increases in lung cancer. In 1928, Lombard and Doering presented initial suspicions of a relationship between tobacco and disease when they noted that heavy smoking was more common among cancer patients than among control groups (7).

In the 1930's, trends in diseases such as lung cancer became evident, promoting the start of intensive inquiries and animal experiments into disease relationships and into the chemical composition and pathogenic effects of tobacco and tobacco smoke. In 1938, Pearl found that heavy smokers had a shorter life expectancy than nonsmokers (9), and 1939 saw the beginnings of large-scale epidemiologic studies of the relationship between tobacco use and lung cancer. A large number of clinical and pathological observations on effects of tobacco smoke on man had accumulated by this time.

The end of the 1930's marked the beginning of almost 40 years of retrospective (case-control) studies on selected diseases suspected of association with tobacco use (primarily lung cancer, chronic bronchitis, emphysema, and coronary artery disease) and prospective studies of diseases and mortality among cohorts of smokers and nonsmokers. By the early 1950's, there had been reports of many significant epidemiologic studies, and four of the seven prospective (cohort) mortality studies had been launched. Tobacco was increasingly being identified as a health hazard. In 1954, a group of tobacco manufacturers, growers, and warehousemen established the Tobacco Industry Research Committee to launch a research program on tobacco use and health.

The accumulation of consistent results from a growing number of studies on lung cancer led the then Surgeon General, Dr. Leroy E. Burney, to instigate the establishment by the National Cancer Institute, the National Heart Institute, the American Cancer Society and the American Heart Association of a scientific study group to assess the problem. The group agreed that a causal relationship between cigarette smoking and lung cancer existed (11); and on July 12, 1957 the Surgeon General placed the Service on record as saying that the weight of evidence indicated a causative relationship between excessive smoking and lung cancer. A brilliant analysis and defense by Cornfield, et al. of the evidence supporting this causal relationship by appeared in 1959 (3). In that year, the U.S. Public Health Service reiterated its position and took one step further when Burney stated that the principal factor in the increased incidence of lung cancer was smoking, particularly smoking of cigarettes (2).

In the early 1960's, a trend toward policies of intervention was hastened and encouraged by a number of events. On June 1, 1961, the presidents of the American Cancer Society, the American Public Health Association, the American Heart Association, and the National

Tuberculosis Association urged President Kennedy to establish a commission to study the tobacco problem. On January 4, 1962, representatives of these organizations met with Surgeon General Luther L. Terry once more to urge action. A proposal from Terry to the Secretary of Health, Education, and Welfare called for an expert advisory committee to assess existing knowledge and make appropriate recommendations. In March, a resolution introduced by Senator Maurine Neuberger (SJR174) called for the establishment of a Presidential commission on tobacco and health, but it was never brought to a vote.

On April 16, the Surgeon General presented a detailed proposal for an advisory group to re-evaluate the 1959 position of the Service. He cited new studies on major adverse health effects, evidence that medical opinion was now very strong against smoking, a request from the Federal Trade Commission for guidance on labeling and advertising of tobacco products, and a recent report of the Royal College of Physicians of London which concluded that "cigarette smoking is a cause of lung cancer and bronchitis and probably contributes to the development of coronary heart disease..." (10).

Consultations between the White House and Public Health Service officials led to Surgeon General Terry's announcement on June 7, 1962, of the planned formation of an expert committee to review all data on smoking and health. Representatives of the American Cancer Society, the American College of Chest Physicians, the American Heart Association, the American Medical Association, the Tobacco Institute, Inc., the Food and Drug Administration, the National Tuberculosis Association, the Federal Trade Commission, and the President's Office of Science and Technology met with the Surgeon General on July 27 to establish the work of the expert committee and to agree on a list of some 150 scientists and physicians qualified to evaluate data on the relationship between tobacco use and health. Terry selected 10 from the list and, thus, the Surgeon General's Advisory Committee on Smoking and Health was launched at its first meeting on November 9, 1962.

The members of the Committee were: Stanhope Bayne-Jones, M.D., L.L.D., Former Dean, Yale School of Medicine; Walter J. Burdette, M.D., Ph.D., University of Utah; William G. Cochrane, M.A., Harvard University; Emmanuel Farber, M.D., Ph.D., University of Pittsburgh; Louis F. Fieser, Ph.D., Harvard University; Jacob Furth, M.D., Columbia University; John B. Hickam, M.D., University of Indiana; Charles LeMaistre, M.D., University of Texas; Leonard M. Schuman, M.D., University of Minnesota; and Maurice H. Seevers, M.D., Ph.D., University of Michigan.

The judgments of the Advisory Committee led to a series of significant conclusions, released in 1964 in the now historic Report of

the Advisory Committee to the Surgeon General of the Public Health Service on Smoking and Health (15):

1. Cigarette-smoking males were found to have a 70 percent excess risk of mortality over nonsmokers. Female smokers were found to have an elevated risk of mortality, but less than that of males.

2. Cigarette smoking was judged to be causally related to lung cancer in men, the magnitude of the effect of cigarette smoking far outweighing all other factors. A similar trend was noted in females, but studies then available presented insufficient grounds for a firm judgment on causality (4). Included as evidence in the judgment of causality were the several findings of a dose-response relationship: The risk of death from lung cancer increased directly with duration of smoking, number of cigarettes smoked per day, inhalation, and, indirectly, with age when smoking began; discontinuance of smoking lowered the risk. For the combined group of pipe, cigar and pipe, and cigar smokers, the risk of lung cancer was greater than for nonsmokers, but was much less than for cigarette smokers.

3. Cigarette smoking was judged to be the most important of the causes of chronic bronchitis in both men and women in the United States and was found to increase the risk of dying from chronic bronchitis and emphysema.

4. Male cigarette smokers were found to have significantly higher death rates from coronary artery disease than nonsmoking males. The data then available were borderline for a judgment of causality by the rigid criteria employed for all disease entities.

5. A causal relationship was not established at the time for a number of other cardiovascular diseases.

6. Significant associations between several other cancer sites and tobacco use were judged to be causal, including pipe smoking and lip cancer, and cigarette smoking and laryngeal cancer.

7. Although the evidence revealed associations between cancer of the oral cavity and the several forms of tobacco use, between such tobacco use and esophageal cancer, and between cigarette smoking and urinary bladder cancer, the data subjected to the judgment criteria did not at that time support a judgment of causality.

A number of other diseases or conditions suggested to be associated with smoking by clinical impressions or by showing excess mortalities in the prospective studies were also scrutinized. They included: peptic ulcer, tobacco amblyopia, cirrhosis of the liver, accidents, influenza and pneumonia, and low infant birth weight.

In the instance of peptic ulcer, epidemiologic studies indicated a consistent excess risk of mortality from peptic ulcer, particularly gastric ulcer, among cigarette smokers, but in 1964 a judgment of causality could not be made.

Tobacco amblyopia had been clinically associated with pipe and cigar smoking, but the Committee could find no substantiation of this

clinical impression, since there had been no epidemiologic studies of this now rare entity and experimental studies had not been adequately controlled.

Cirrhosis of the liver had been found to contribute to excess mortality among cigarette smokers in the seven prospective studies. However, because of the relationship of alcohol consumption (and nutritional deficiencies) to cirrhosis, the correlation of heavy drinking with heavy smoking, and lack of definitive studies on the compartmentalization of these two factors at the time, there was inadequate support of a causal association.

As for accidents, an obvious relationship between smoking and fires in the home was noted in 1964.

A moderate excess risk of mortality from influenza and pneumonia was noted in six of the seven prospective studies but this association had not been evaluated by further studies. Other acute respiratory illnesses had been studied in families and in college graduates and no differences had been found between cigarette smokers and nonsmokers.

There had been some interest in the relationship between maternal smoking during pregnancy and pregnancy outcome. By 1964, five retrospective and two prospective studies revealed an association of cigarette smoking during pregnancy with lower birth weight and premature deliveries. A relationship with fetal and/or neonatal death was deemed equivocal at the time.

Finally, although smokers were found to differ from nonsmokers in a number of ways, none of the studies appraised by the Advisory Committee revealed any single variable discriminating significantly between the two groups. The report emphasized that "the overwhelming evidence points to the conclusion that smoking—its beginning, habituation and occasional discontinuance—is to a large extent psychologically and socially determined."

The Committee concluded: "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action."

The release of the Advisory Committee's Report to the Surgeon General stimulated many studies and reports, the data from which augmented the earlier studies, strengthened the conclusions of the Committee, provided information in areas for which data had not existed, and shed light on the pathogenetic mechanisms of the thousands of compounds in tobacco and tobacco smoke. These studies were epidemiologic, clinical, experimental, and, in the area of smoking control, psychologic and sociologic as well.

The Federal Cigarette Labeling and Advertising Act of 1965 (P.L. 89-92) required the Secretary of Health, Education, and Welfare to submit regular reports to Congress on the health consequences of smoking, together with legislative recommendations. The purpose was

to monitor the scientific literature on smoking and health. This surveillance of world literature was performed by the National Clearinghouse for Smoking and Health (now succeeded by the Office on Smoking and Health). The updated reports were issued in 1967, 1968, 1969, 1971, 1972, 1973, 1974, 1975, 1976, and 1978.

This current 15th anniversary volume on smoking and health is offered as a detailed review and reappraisal of smoking and health relationships. Its contents are the work of numerous scientists both within and outside the Department of Health, Education, and Welfare. All are acknowledged elsewhere.

On the following pages, this introductory chapter seeks to summarize the principal findings and extensions of knowledge contributed by the scientific community over these 15 years. An attempt has been made to highlight particularly the earlier gaps in knowledge that have been closed or shortened in the intervening period.

Summary

Health Consequences of Smoking

Mortality

This 1979 appraisal strengthens earlier conclusions as to the relationship between smoking and mortality. Materials reviewed include the seven original prospective studies and new data derived from long-term follow-up of three of these investigations: the British doctors' study (20 years), the Hammond study (12 years) and that initiated by Dorn (16 years). Also reviewed are data from Japanese and Swedish prospective studies. The overall findings yield quantitative results over time which are substantially identical with earlier conclusions. These findings include:

1. The overall mortality ratio for all male current cigarette smokers, irrespective of quantity, is about 1.7 (70 percent excess) compared to nonsmokers.
2. Mortality ratios increase with amount smoked. The two-pack-a-day male smoker has a mortality ratio of 2.0 compared to nonsmokers.
3. Overall mortality ratios are directly proportional to the duration of cigarette smoking. The longer one smokes, the greater the risk of dying.
4. Overall mortality ratios are higher for those who initiated their cigarette smoking at younger ages compared to those who began smoking later.
5. Overall mortality ratios are higher among cigarette smokers who inhale than among those who do not.
6. Although mortality ratios for smokers are highest at the younger ages and decline with increasing age, the actual number of excess deaths attributable to cigarette smoking increases with age.

7. Former cigarette smokers experience declining overall mortality ratios as the years of discontinuance increase. After 15 years of cessation, mortality ratios for former cigarette smokers are similar to those who never smoked. Although mortality ratios for any given age for former smokers are directly proportional to the amount smoked before cessation and inversely related to the age of smoking initiation, cessation of smoking does diminish such individuals' risk regardless of these former factors, provided they are not ill at time of cessation. (Actually, the mortality ratios among those who had discontinued smoking less than 1 year before enrollment in several of the prospective studies were higher than for current cigarette smokers. This was also manifest in the total mortality rates for former cigar and pipe smokers. Further analyses separating those who stopped smoking because of illness from those ex-smokers who stopped for other reasons revealed higher mortality rates among the former.)

8. Cigar smoking is not without risk of increased mortality. The overall mortality ratios for cigar smokers are somewhat higher than for nonsmokers and are directly proportional to the number of cigars smoked per day.

9. Pipe smoking seems to have a slight effect in increasing overall mortality, but individuals who combine their pipe smoking (or cigar smoking) with cigarette smoking experience a level of risk of mortality intermediate between those who smoke only pipes or cigars and those who smoke only cigarettes.

A number of new findings in the relationship between smoking and overall mortality were found over the 15-year interval:

1. Calculations from prospective study data have indicated that life expectancy at any given age is significantly shortened by cigarette smoking. For example, a 30- to 35-year-old, two-pack-a-day smoker has a life expectancy 8 to 9 years shorter than a nonsmoker of the same age.

2. Overall mortality ratios increase with the "tar" and nicotine content of the cigarette. For smokers of low "tar" and nicotine cigarettes (less than 1.2 mg nicotine and less than 17.6 mg "tar"), overall mortality ratios are 50 percent greater than for nonsmokers, and 15 to 20 percent less than for all smokers of cigarettes.

3. For the 1964 report, data were inadequate for firm judgments on the mortality status of female cigarette smokers. Adequate follow-up in the prospective studies during these past 15 years has revealed mortality ratios for female cigarette smokers somewhat less than those for male smokers. This difference is deemed to be due to differences in exposure (later age of initiation, fewer cigarettes per day, and use of cigarettes with lower "tar" and nicotine content). Female dose-responses (quantity, age at initiation, duration of smoking, inhalation, "tar" and nicotine content) are the same as for male cigarette smokers.

Subsets of females with smoking characteristics similar to those of men experience mortality rates similar to those of male smokers.

4. From the detailed data of two prospective studies (Hammond and Dorn) the excess in mortality is noted to be greatest for the 45- to 54-year age groups among men and women. Thus, smoking mortality is premature mortality.

Cause-Specific Mortality

1. Although mortality ratios are particularly high among cigarette smokers for such diseases as lung cancer, chronic obstructive lung disease, and cancer of the larynx, coronary heart disease is the chief contributor to the excess mortality among cigarette smokers.

2. Lung cancer and chronic obstructive lung disease, in that order, follow after coronary heart disease in accounting for the excess mortality.

3. Pipe and cigar smoking are associated with elevated mortality ratios for cancers of the upper respiratory tract, including cancer of the oral cavity, the larynx, and the esophagus.

Morbidity

Following the 1964 Report to the Surgeon General, the National Center for Health Statistics began collecting information on smoking as part of the National Health Interview Survey. On the basis of probability samples of the population, estimates can be made for the general population. These data have proven valuable in assessing the relationships between tobacco use and illnesses, disability, and other health indicators. The findings include:

1. In general, male and female current cigarette smokers tend to report more chronic conditions, such as chronic bronchitis and/or emphysema, chronic sinusitis, peptic ulcer disease, and arteriosclerotic heart disease, than persons who never smoked.

2. A dose-response gradient was noted with the amount of cigarettes smoked per day for most of the chronic conditions. Particularly impressive is the gradient for chronic bronchitis and/or emphysema, with an increase in prevalence among male smokers of two packs or more a day to four times that of those who have never smoked, and among female smokers of two packs or more, to 10 times that of those who never smoked.

3. The age-adjusted incidence of acute conditions (e.g., influenza) for males who had ever smoked was 14 percent higher, and for females 21 percent higher, than for those who had never smoked cigarettes.

4. Indicators of morbidity which are not dependent upon physicians' diagnoses include measures of disability such as work-days lost, days in bed, and days of limitation of activity resulting from chronic diseases.

- (a) Male current smokers of cigarettes reported a 33 percent excess, and female current smokers a 45 percent excess, of work days lost in comparison to persons who never smoked. Male former smokers had an excess of 41 percent, and female former smokers an excess of 43 percent, of work days lost. From the 1974 survey data, this calculates to more than 81 million excess days of work lost for the U.S. population in 1 year.
 - (b) Male current smokers had a 14 percent excess, and female current smokers a 17 percent excess, of days of bed disability over those who never smoked. Smokers in all age and sex groups, except for women over age 65, reported more days in bed due to illnesses than did persons who never smoked. From 1974 data, this calculates to more than 145 million excess days of bed disability for the U.S. population in 1 year.
 - (c) The excesses of disability measures are dose-related.
 - (d) For most age and sex groups, a higher proportion of current and former smokers report longer limitation of activity due to chronic diseases than do persons who never smoked.
5. A tendency was noted for higher proportions of former smokers and those who never smoked, as compared to present smokers, to assess their own health status as excellent.
6. Current smokers and former smokers reported more hospitalizations than nonsmokers in the year prior to interview. Data on the reasons for these hospitalizations have not been analyzed.

While most studies show a reduction in the risk of mortality among former smokers, data on disability and illness often show continued high risk among former smokers. This finding should be interpreted more as an indication of the need for both additional data and further analysis of existing data, rather than as an indication of the lack of a beneficial impact on health status from smoking cessation.

These findings on morbidity are consistent with the vast amount of evidence on the relationship between cigarette smoking and mortality.

Cardiovascular Diseases

The tremendous amount of research on the relationship between cardiovascular disease and smoking, undoubtedly stimulated by a lack of adequate information in the areas of the nature of atherosclerosis, the mechanisms of atherogenesis, and the pathogenetic pathways for smoking components, has provided a basis for firmer judgments on the relationship than could be made in 1964. The present report on cardiovascular disease and smoking draws heavily on the 1976 reference report on smoking and health (14) and adds more recent data.

Systematic observations on the association between smoking and cardiovascular diseases have been made on considerably more than a

million individuals in the United States (the majority on men) and have involved many millions of person-years of experience.

Sample sizes are now extensive in both retrospective and prospective studies. Variables observed in retrospective studies have been relatively limited; in some prospective studies, they have been more numerous and have allowed for complex analyses in which the independence of smoking as a risk factor among other risk factors has been defined. Autopsy and experimental studies in animals have also been extended and serve to clarify earlier issues.

The 1979 Report includes the following conclusions:

1. The data collected from Western countries, particularly the United States, but also the United Kingdom, Canada, and others, show that smoking is one of three major independent risk factors for heart attack manifested as fatal and nonfatal myocardial infarction and sudden cardiac death in adult men and women. Moreover, the effect is dose-related, synergistic with other risk factors for heart attack, and of stronger association at younger ages.

2. Smoking cigarettes is a major risk factor for arteriosclerotic peripheral vascular disease and is strongly associated with increased morbidity from arteriosclerotic peripheral vascular disease and with death from arteriosclerotic aneurysm of the aorta.

3. The data establish adequately that cigarette smoking is associated with more severe and extensive atherosclerosis of the aorta and coronary arteries than is found among nonsmokers. The effect is dose-related.

4. Epidemiologic data on the association between cigarette smoking and angina pectoris and cerebrovascular disease manifested as stroke are not conclusive.

5. Smoking increases the possibility of a heart attack recurrence among survivors of a myocardial infarction.

6. In acute experiments on arteriosclerotic patients with angina pectoris or with intermittent claudication of peripheral vascular disease, smoking or exposure to carbon monoxide reduces the patient's established threshold for the precipitation of angina or claudication. Both nicotine and carbon monoxide (CO) aggravate exercise-induced angina.

7. Women who smoke and use oral contraceptives are at a significantly elevated risk for fatal and nonfatal myocardial infarction. A synergistic role of cigarette smoking and oral contraceptive use is suggested for subarachnoid hemorrhage.

8. Smokers of low "tar" and nicotine cigarettes experience less risk for coronary heart disease than smokers of high "tar" and nicotine cigarettes, but their risk is considerably greater than that of nonsmokers.

9. Cigarette smoking does not induce chronic hypertension. However, in the presence of hypertension as a risk factor for coronary heart

disease, smoking acts synergistically to increase the effective risk by joining the risks attributable to hypertension and to smoking alone.

10. Cigarette smoking is a major risk factor for ischemic peripheral vascular disease of arteriosclerotic type; cigarette smoking increases appreciably the risk of peripheral vascular disease in diabetes mellitus.

11. Cessation of cigarette smoking improves the prognosis of arteriosclerotic peripheral vascular disease and is advantageous to its surgical treatment.

12. Cessation of smoking reduces the risk of mortality from coronary heart disease, and after 10 years off cigarettes this risk approaches that of the nonsmoker.

13. The relationship of smoking to the incidence of stroke is not established; however, an association with subarachnoid hemorrhage has been reported in women.

In summary, for the purposes of preventive medicine, it can be concluded that smoking is causally related to coronary heart disease for both men and women in the United States .

Cancer

The strongest evidence of a causal relationship between tobacco use and disease was delineated for lung cancer in the 1950's and 1960's and subjected to the rigid criteria of appraisal in the 1964 Report. In the intervening years, additional epidemiological, clinical, autopsy, and experimental studies have augmented and strengthened the earlier conclusions, particularly with regard to women smokers, for whom only preliminary data were then available.

New evidence has also accumulated since 1964 with respect to the relationships between tobacco use and cancer of the larynx, oral cavity, esophagus, urinary bladder, kidney, and pancreas.

In the case of laryngeal cancer, the accumulated evidence since 1964 has strengthened, but not materially changed, the conclusions of the 1964 Report.

In the case of cancer of the oral cavity, the 1964 Report had to base its conclusions primarily on retrospective studies because of the diversity of sites, their varying incidence of tobacco exposure, and the relatively small numbers derivable in the early years of the prospective studies. These studies, unfortunately, varied in approach and either did not separate the several sites of the oral cavity or found the classes of smoking too numerous for testing their significance. Thus, the only firm judgment which could then be made was that a causal relationship exists between pipe smoking and cancer of the lip.

The 1964 Report found that an association existed between tobacco use and esophageal and urinary bladder cancer, but the Committee could not determine from the available data whether there was a causal relationship.

The 1964 Report did not address kidney or pancreatic cancer. While retrospective studies were not examined, the seven prospective studies indicated that the average mortality ratio for kidney cancer was 1.5.

Present knowledge about the relationship between smoking and the various cancers is summarized below, excerpted from the conclusions to be found in Chapter 5. As will be seen, the evidence is now overwhelming.

Lung Cancer

1. Cigarette smoking is causally related to lung cancer in both men and women.

2. The risk of developing lung cancer is increased with increasing dosages of smoking as measured by: number of cigarettes smoked per day, duration of smoking, age of initiation of smoking, degree of inhalation, "tar" and nicotine content of cigarettes smoked, and several other measurements.

3. Lung cancer mortality rates in women are increasing more rapidly than in men and, if present trends continue, will be the leading cause of cancer death in women in the next decade.

4. Use of filter cigarettes and smoking of cigarettes with lower amounts of "tar" and nicotine decrease lung cancer mortality rates among smokers; however, these rates are significantly elevated compared to rates for nonsmokers.

5. Ex-smokers experience decreasing lung cancer mortality rates which approach the rates of nonsmokers after 10 to 15 years of cessation. The residual risk of developing lung cancer in ex-smokers is proportional to the overall dosage of lifetime cigarette-smoking exposure, and inversely related to the interval since cessation.

6. Pipe and cigar smokers have lung cancer mortality rates above nonsmokers, but these rates are lower than those for cigarette smokers.

7. Certain occupational exposures can act synergistically with smoking to significantly increase lung cancer mortality rates far above those resulting from either exposure alone.

Cancer of the Larynx

8. Cigarette smoking is a significant causative factor in the development of cancer of the larynx in men and women and is directly related to several measures of dosage.

9. Pipe and cigar smokers experience approximately the same risk as cigarette smokers for cancer of the larynx.

10. There appears to be a synergistic effect between smoking and alcohol intake, as well as between asbestos exposure and smoking, for laryngeal cancer.

11. There is a substantial decrease in the risk of developing cancer of the larynx with long-term use of filter cigarettes compared to the use of nonfilter cigarettes; ex-smokers, after 10 years of cessation, have mortality rates which approximate those of nonsmokers.

Oral Cancer

12. Epidemiological studies indicate that smoking is a significant causal factor in the development of oral cancer. The risk increases with the number of cigarettes smoked per day.

13. Pipe and cigar smokers experience almost the same high risk for oral cancer as experienced by cigarette smokers.

14. A synergism exists between smoking and alcohol consumption for oral cancer.

Cancer of the Esophagus

15. Cigarette smoking is a causal factor in the development of cancer of the esophagus, and the risk increases with the amount smoked.

16. The risk of esophageal cancer for pipe and cigar smokers is about the same as that for cigarette smokers.

17. A synergism also exists for esophageal cancer and the marked use of alcohol and cigarette smoking.

Cancer of the Urinary Bladder

18. Epidemiological studies have demonstrated a significant association between cigarette smoking and bladder cancer in both men and women.

19. Cigarette smoking acts independently and synergistically with other factors, such as occupational exposures, to increase the risk of developing cancer of the urinary bladder.

Cancer of the Kidney

20. Cigarette smoking is associated with cancer of the kidney for men. No data exist to substantiate a relationship for women.

Cancer of the Pancreas

21. Cigarette smoking is related to cancer of pancreas, and several epidemiological studies have demonstrated a dose-response relationship.

Experimental Studies

22. Experimental studies on a variety of animal models have confirmed the carcinogenic effects of tobacco smoke and its constituents on several sites including lung, larynx, esophagus, and oral cavity.

Non-Neoplastic Bronchopulmonary Diseases

Of the non-neoplastic bronchopulmonary diseases, only chronic bronchitis was judged to be causally related to cigarette smoking in the 1964 Report. In fact, cigarette smoking was then deemed the most important cause of chronic bronchitis in the U.S. and a cause of increased risk of mortality from chronic bronchitis. A relationship to pulmonary emphysema was deemed to exist, but a causal interpretation of this relationship could not then be ascribed. Cigarette smoking was then judged to exceed atmospheric pollution and environmental exposures as a cause of chronic obstructive lung disease (COLD). These diseases rank second only to coronary artery disease as a cause of Social Security-compensated disability.

In the 15 intervening years, the updating of several of the larger prospective studies and numerous retrospective and cross-sectional studies have strengthened the conclusions of the 1964 Report.

1. Cigarette smokers have a higher prevalence of chronic bronchitis and emphysema than nonsmokers and have an increased chance of dying from these diseases compared to nonsmokers. These risks are significant for both men and women who smoke, although higher rates generally exist for men than women.

2. Cigarette smokers have an increased frequency of respiratory symptoms, and at least two of them, cough and sputum production, are dose-related.

3. Pulmonary function abnormalities, as measured by various tests, are greater among cigarette smokers than nonsmokers.

4. Impairment of pulmonary function can be detected among smokers even in young age groups, and respiratory symptoms can be demonstrated in teenagers and adolescents who smoke.

5. Cigar and pipe smokers show higher mortality rates for chronic bronchitis and emphysema than nonsmokers, but these rates are not as great as those for cigarette smokers.

6. Cessation of smoking definitely improves pulmonary function and decreases the prevalence of respiratory symptoms. Cessation reduces the chance of premature death from chronic bronchitis and emphysema.

7. Although the majority of studies demonstrate a higher prevalence of pulmonary function abnormalities in smokers when compared to nonsmokers, conflicting data make it difficult to substantiate racial differences among smokers and nonsmokers.

8. Autopsy data have demonstrated more frequent abnormalities in macroscopic and microscopic lung sections among smokers compared to nonsmokers, and these effects were dose-related.

9. Several mechanisms have been suggested by which smoking might induce lung damage, including an imbalance of protease-antiprotease.

10. A wide variety of alterations in the immune system have been observed due to cigarette smoking. These alterations include macro-

phages from smokers responding abnormally to migration inhibitory factor (MIF) or antigen challenges, and T lymphocytes in smokers showing a diminished response to phytohemagglutinin (PHA), compared to those of nonsmokers. However, the role of these alterations in lung damage is unclear at this time.

11. Individuals with severe alpha-1-antitrypsin deficiency have an excess risk for developing emphysema, and the onset of symptoms is probably abbreviated in these persons by smoking. It is unclear if individuals with mild deficiency represent a group at special risk.

12. Other genetic factors may play a role in determining the risk for COLD, but these are far outweighed by the effect of cigarette smoking.

13. Certain occupations, primarily those exposing workers to dusty occupational environments, are related to COLD, and this relationship is increased further by cigarette smoking. In none of these studies are occupational effects as strong as smoking.

14. Although an increased risk of COLD due to air pollution probably exists, it is small compared to that due to cigarette smoking under conditions of air pollution to which the average person is exposed.

15. Childhood respiratory disease appears to be a risk factor for respiratory symptoms as an adult. However, cigarette smoking appears to be a more important factor in increasing the risk for developing these symptoms.

Interaction Between Smoking and Occupational Exposures

An extensive review of the literature on lung cancer in chromium and nickel workers and in uranium miners was prepared (12) for the 1964 Advisory Committee. Other studies had examined the relationships among coal gas and asbestos workers as well as in exposures to arsenic, hematite, isopropyl oil, beryllium, and copper. Significant excess lung cancer mortality was noted for chromate, nickel, coal gas and asbestos workers and for uranium miners; exposure to arsenic, hematite, beryllium, and copper remained suspect.

At the time of the 1964 report it was noted that "it must be emphasized quite strongly that the population exposed to industrial carcinogens is relatively small" (compared to the size of the smoking population), "and that these agents cannot account for the increasing lung cancer risk in the general population." It was further noted: "Of greater importance is the regrettable fact that in none of these occupational hazard studies were smoking histories obtained. Thus the contribution which smoking, as a contributory or etiologic factor, may have made to the lung cancer picture in these risk situations is unknown"(15).

Despite increasing recognition that smoking and occupational exposures may each contribute to the development of certain disease

states, few investigators have addressed the ways in which these two factors act together to produce disease.

This chapter has identified and illustrated six ways in which smoking may act in combination with physical and chemical agents found in the workplace to produce or increase a broad spectrum of adverse health effects. The six modes of action listed below are not mutually exclusive and several may prevail for any given agent. They may be compounded by occupational exposure to multiple chemical and physical agents.

1. Tobacco products may serve as vectors by becoming contaminated with toxic agents found in the workplace, thus facilitating entry of the agent into the body by inhalation, ingestion, and/or skin absorption.

2. Workplace chemicals may be transformed into more harmful agents by smoking. Illustrative of this effect is the association between polymer fume fever and smokers as a result of cigarette contamination in the workplace.

3. Certain toxic agents in tobacco products and/or smoke may also occur in the workplace, thus increasing exposure to the agent. Carbon monoxide levels in the occupational environment, for example, add to already high blood carbon monoxide levels found in smokers.

4. Smoking may contribute to an effect comparable to that which can result from exposure to toxic agents found in the workplace, thus causing an additive biological effect. For example, exposure to coal dust may increase a smoker's risk of developing disease.

5. Smoking may act synergistically with toxic agents found in the workplace to cause a much more profound effect than that anticipated simply from the separate influence of the agent and smoking added together. For example, cigarette smoking and exposure to asbestos may interact synergistically to greatly increase the risk of lung cancer.

6. Smoking may contribute to accidents in the workplace.

Those who have the highest risk for occupational exposures to toxic agents in general also have the highest smoking rates. Surveys have shown male blue-collar workers are much more likely to smoke than male white-collar workers. From 1920 to 1966, tobacco consumption increased as did the introduction into the workplace of chemicals with unstudied biological effects. During this same time period, the mortality rates for certain disease states associated with smoking and occupational exposures continued to increase. Some of the effects historically attributed to smoking may actually reflect interactions between smoking and occupational exposures.

Curtailement of smoking in the workplace should be accompanied by simultaneous control of occupational exposures to toxic physical and chemical agents.

Pregnancy and Infant Health

The 1964 report devoted approximately one printed page, including bibliography, to a discussion of the findings of five retrospective and two prospective studies on birth weight of infants born to mothers who smoked during pregnancy. Such infants tended to have a lower birth weight. The mechanism and its biologic significance were then not known and the findings were in some instances controversial. Since then, this area of scientific investigation has resulted in the amassing of significant data which provide many insights into the mechanisms of pathogenesis. The following conclusions are based on the work during this period:

Birth Weight and Fetal Growth

1. Babies born to women who smoke during pregnancy are, on the average, 200 grams lighter than babies born to comparable women who do not smoke. Distribution of birth weights of smokers' babies is shifted downward, and twice as many of these babies weigh less than 2,500 grams, compared with babies of nonsmokers. There is abundant evidence that maternal smoking is a direct cause of the reduction in birth weight.

2. Birth weight is affected by maternal smoking independently of other determinants of birth weight. The more the mother smokes, the greater the baby's birth-weight reduction.

3. The ratio of placental weight to birth weight increases with increasing levels of maternal smoking. This increase may signify a response to reduced oxygen availability due to carbon monoxide and may have some survival value for the fetus.

4. There is no overall reduction in the duration of gestation with maternal smoking, indicating that the lower birth weight of smokers' infants is due to retardation of fetal growth.

5. The pattern of fetal growth retardation that occurs with maternal smoking is a decrease in all dimensions; body length, chest circumference, and head circumference are smaller if the mother smokes.

6. According to studies of long-term growth and development, smoking during pregnancy may affect physical growth, mental development, and behavioral characteristics of children at least up to the age of 11.

7. Overwhelming evidence indicates that maternal smoking during pregnancy affects fetal growth rate directly and that fetal growth rate is not due to characteristics of the smoker rather than to the smoking, nor is it mediated by reduced maternal appetite, eating, and weight gain.

Perinatal Mortality

1. When adjustments are made for age-parity differences in mothers, their socio-economic status, and previous pregnancy histories, the risk of perinatal mortality attributable to smoking is highly significant, independent of these factors, and is dose-related.

2. Maternal smoking increases the risk of fetal death through maternal complications such as abruptio placenta, placenta previa, antepartum hemorrhage, and prolonged rupture of membranes.

3. Although maternal smoking does not produce a lowering of mean gestational age, preterm births are increased in frequency among smokers, and a large proportion of the neonatal deaths occur among these preterm births.

4. Smoking by pregnant women contributes to the risk of their infants being victims of the "sudden infant death syndrome."

5. Maternal smoking can be a direct cause of fetal or neonatal death in an otherwise normal infant. The immediate cause of most smoking-related fetal deaths is probably anoxia, which can be attributed to placental complications with antepartum bleeding in 30 percent or more of the cases. In other cases, the oxygen supply may simply fail from reduced carrying capacity and reduced unloading pressures for oxygen caused by the presence of carbon monoxide in maternal and fetal blood. Neonatal deaths occur as a result of the increased risk of early delivery among smokers, which may be secondarily related to bleeding early in pregnancy and premature rupture of membranes. Considerable literature has appeared in the area of clinical and animal experimental studies on the role of tobacco smoke, nicotine, and carbon monoxide, providing evidence for pathogenetic pathways accounting for both lower birth weight and fetal death.

6. The accumulated evidence does not support a conclusion that maternal smoking increases the incidence of congenital malformations.

Lactation and Breast Feeding

1. The epidemiologic studies on adequacy of lactation do not provide data for a conclusion on the effect of maternal smoking.

2. Although some animal studies reveal diminished milk production (but no reduction in release) following nicotine administration, human experimental studies have not thus far produced evidence for a reduction in lactation with forced smoking of large numbers of cigarettes over short periods of time.

3. There does exist a direct dose-response relationship between the number of cigarettes smoked and nicotine in breast milk.

4. Further detailed research in this area is imperative.

Peptic Ulcer Disease

The 1964 Report appraised the evidence for a relationship between tobacco use and peptic ulcer disease in five retrospective and the seven prospective studies (mortality) and concluded that only an association existed, particularly for gastric ulcers. The biological meaning of this association was not clear, particularly since studies of the effects of cigarette smoking on secretory activity and gastric motility were not consistent.

For the current report, two of the prospective mortality studies have been updated. Peptic ulcer disease mortality has continued to show excesses among smokers of cigarettes.

A number of additional studies of peptic ulcer disease and smoking were also addressed. Five of these studies showed a higher proportion of smokers among ulcer patients than among controls. Six studies showed a greater prevalence among male cigarette smokers than nonsmokers, the median ratio being 1.7. The findings in women are comparable. The majority of studies provided evidence of increased frequency of peptic ulcer disease with increases in the amount smoked.

Experimental and clinical studies of gastric and pancreatic secretion and pyloric reflux were extended in this period to resolve the mechanism of action of smoking on occurrence of peptic ulcer disease.

On the basis of the research data surveyed, it is concluded:

1. Epidemiological studies have found that cigarette smoking is significantly associated with the incidence of peptic ulcer disease and increases the risk of dying from peptic ulcer disease. This risk is, on the average, twice as high for smokers compared to nonsmokers, and appears to be greater for gastric than for duodenal ulcer disease.

2. The risk of peptic ulcer disease is dose-responsive and exists for both men and women.

3. While the pathogenetic mechanisms have not been clearly elucidated, the association between smoking and peptic ulcer disease is significant enough to suggest a causal relationship.

4. Evidence that smoking retards healing of peptic ulcers is highly suggestive.

5. Pipe smoking appears unrelated to peptic ulcer disease.

6. Experimental and clinical studies on the effect of smoking on pancreatic secretion and pyloric reflux suggest mechanisms by which peptic ulcer disease may develop.

Allergy and Immunity

Allergic manifestations to tobacco, its smoke, or its extracts were not reviewed in the 1964 report. Various studies in the late 1960's and 1970's probed the relationship of smoking to immunologic mechanisms and immune responses, not only in the acute infectious diseases, but also in several of the chronic diseases such as pulmonary disease.

The following is a summary of this research and our current understanding of this facet of human illness in relation to tobacco use.

1. Tobacco and tobacco smoke extracts have been found to act as antigens, including both precipitating and reaginic antibodies, in animals and man. These tobacco products can also sensitize lymphocytes participating in cell-mediated immune functions.

2. Tobacco and its combustion products present such an array of natural and derived components, additives, and contaminants that the precisely defined role for tobacco in immune and allergic processes cannot be delineated.

3. Several tobacco antigens have been isolated. However, epidemiologic studies on the frequency of true allergy to tobacco are inconclusive.

4. Tobacco smoke exerts a variety of effects on respiratory tract structures, and chronic smoking leads to consistent histologic changes in the respiratory tract.

(a) Evidence indicates an adverse long-term effect on the mucociliary transport mechanisms and mucus composition.

(b) The number of macrophages isolated from smokers' lung fluid is increased compared to nonsmokers.

(c) Changes in the ultrastructure of macrophages are observed in smokers.

(d) Alveolar macrophages from smokers have altered metabolism and measurable degrees of physiologic impairment.

5. Alterations in assays of cell-mediated immunity are noted locally and systemically in smokers.

6. Leukocytosis and reversible hypereosinophilia have been seen in smokers.

7. Allergic individuals, particularly those with rhinitis or asthma, may be more sensitive to the nonspecific effects of cigarette smoke than healthy individuals.

8. Because the ability to make a definitive diagnosis of tobacco allergy is complicated by the difficulty in demonstrating a cause and effect relationship between immunologic events and disease manifestations, additional evidence is required to establish a definitive role for tobacco sensitization in causing allergic disease.

Involuntary Smoking

The effects of involuntary smoking (passive or second-hand smoking) on the nonsmoker were not examined or appraised in the 1964 report but were initially discussed in the 1972 report, *The Health Consequences of Smoking*, and updated in the 1975 edition. The current report's findings in this area are summarized below. It should be understood that the literature is of recent vintage and only a limited amount of systematic information regarding the health effects of involuntary smoking on the nonsmoker is available.

1. Sidestream smoke, which comes from the lighted tip of the cigarette between puffs, has higher concentrations of some of the irritating and hazardous substances than does mainstream smoke (that smoke inhaled by the smoker).

2. Children of parents who smoke are more likely to have bronchitis and pneumonia during the first year of life; this effect is independent of social class, birth-weight, and parental cough and phlegm production.

3. Simple extrapolation of dose-response relationships, which are traditionally used in assessing the hazards of smoking to the smoker, cannot be employed in assessing hazards in nonsmokers.

4. Cigarette smoking in enclosed spaces can produce carbon monoxide (CO) levels well above the Ambient Air Quality Standard (9 ppm) even where ventilation is adequate.

5. Substantial proportions of the population experience irritation and annoyance when exposed to cigarette smoke. The eyes and nose are most sensitive to irritation, and such irritation increases with increasing levels of smoke contamination. Unrestricted smoking on buses and planes annoys the majority of nonsmoking passengers even under conditions of adequate ventilation.

6. Little or no physiological response to smoke was detected in healthy nonsmokers exposed to cigarette smoke. Higher heart rates detected may be due to psychological factors.

7. A slight reduction in maximum exercise capacity was noted in older nonsmokers exposed to levels of CO occasionally found in involuntary smoking situations.

8. Changes in psychomotor function, especially attentiveness and cognitive function, at levels of CO found in involuntary smoking conditions have been noted, but these effects are measurable only at the threshold of stimuli perception.

9. Levels of COHb produced by involuntary smoking situations are functionally insignificant in healthy individuals.

10. Levels of carbon monoxide which can be reached in cigarette smoke-filled environments have been shown to decrease the exercise duration required to induce angina pectoris in patients with coronary artery disease. These levels of CO also have been shown to reduce the exercise time until onset of dyspnea in patients with hypoxic chronic lung disease.

Interactions of Smoking with Drugs, Food Constituents, and Responses to Diagnostic Tests

The pervasiveness of tobacco use in our society and the frequency of altered disposition and pharmacological effects of many common drugs on smokers make it apparent that cigarette smoking is one of the primary causes of drug interactions in humans. An assessment of the literature in this area provides the following conclusions: