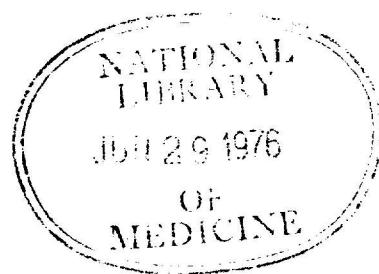


The  
Health Consequences  
of SMOKING  
1975



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of SMOKING  
1975

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
Center for Disease Control  
Atlanta, Georgia 30333



July 23, 1975

Honorable Carl Albert  
Speaker of the House of Representatives  
Washington, D.C. 20515

Dear Mr. Speaker:

As required by Section 8(a) of the Public Health Cigarette Smoking Act of 1969, enclosed is the 1975 report on the health consequences of smoking. The recent scientific information reviewed in the report reaffirms the previous evidence that cigarette smoking is a serious public health problem. It is a major contributor to the development of cardiovascular disease, various types of cancer, and respiratory disease. Its toll in illness and premature death is needless and preventable. The recent literature further refines our understanding of the mechanisms by which smoking influences these disease states.

Under this Act, I am also required to submit to you such recommendations for legislation as I deem appropriate. This Department has previously taken a position in support of legislation which would authorize the regulation of cigarettes through the power to ban the manufacture and sale of cigarettes exceeding what are considered excessively hazardous levels of tar, nicotine, carbon monoxide, and other ingredients shown to be injurious to health. The extent to which the cigarette smoking public has over the years spontaneously moved towards this kind of self protection suggests that it would welcome the additional protection such legislation would bring. This Department, therefore, recommends to the Congress that it consider legislation providing this Department or some other appropriate agency with the authority to set maximum permissible levels of hazardous ingredients in cigarettes.

With kindest regards.

Sincerely,

Caspar W. Weinberger  
*Secretary*

Enclosure

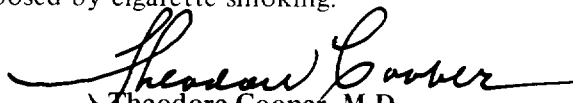
## PREFACE

Each year the Public Health Service reviews the scientific data related to the health consequences of smoking and submits its review to the Congress. This report, the ninth in the series, summarizes recent research in four major areas: cardiovascular disease, cancer, respiratory disease, and the effects of smoking on the nonsmoker who shares the environment of those who smoke.

As has been the case with each of the previous reports in the series, the research summarized herein further confirms the relationships between cigarette smoking and disease and premature death and refines our understanding of the mechanisms underlying these relationships.

Cigarette smoking remains the largest single unnecessary and preventable cause of illness and early death. In the eleven years since the report of the Advisory Committee to the Surgeon General in 1964, there has been progress toward reducing this toll. Millions of Americans have stopped smoking cigarettes, and millions more have not taken up smoking. Even for those who continue to smoke, there has been a striking reduction in the "tar" and nicotine content of cigarettes used by the vast majority. At the same time, however, counter-balancing these gains, there has been an increase in cigarette smoking by women and young people, especially teen-age girls.

To eliminate the needless death and disability attributable to cigarette smoking, the Public Health Service remains committed today, as in the past, to increasing the knowledge about the health consequences of smoking and to educating the American people as to the nature and extent of the hazards of smoking. This is a task, not for government alone, but for the great institutions of society as a whole — the family, the schools, the health care system. Through concerted effort, a climate of respect for our own health and that of others can be created. Such a climate must certainly be conducive to reducing and eventually eliminating the needless burden of disease and premature death imposed by cigarette smoking.

  
Theodore Cooper, M.D.  
*Assistant Secretary for Health*

June 1975

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## PREPARATION OF THE REPORT AND ACKNOWLEDGMENTS

### *Previous Reports*

Reviews of the scientific evidence linking smoking to health effects began in 1964 with *Smoking and Health, Report of the Advisory Committee to the Surgeon General of the Public Health Service* or as subsequently referred to “the Surgeon General’s Report.” After this report, Public Law 89-92 was passed requiring supplemental reports to Congress on this subject. In compliance, three reports were submitted:

1. *The Health Consequences of Smoking, A Public Health Service Review: 1967.*
2. *The Health Consequences of Smoking, 1968 Supplement to the 1967 PHS Review.*
3. *The Health Consequences of Smoking, 1969 Supplement to the 1967 PHS Review.*

In April 1970, Public Law 91-222 amended the previous law and called for an updated report on the health effects of smoking no later than January 1, 1971, with annual reports thereafter. *The Health Consequences of Smoking, A Report of the Surgeon General: 1971*, a comprehensive review of all the scientific literature available to the National Clearinghouse for Smoking and Health and with emphasis on the most recent additions to the literature, was that updated report. Since then, the following annual reports on the health consequences of smoking have been submitted:

1. *The Health Consequences of Smoking, A Report of the Surgeon General, 1972.*
2. *The Health Consequences of Smoking, 1973.*
3. *The Health Consequences of Smoking, 1974.*

Each report since the original “Surgeon General’s Report” has reviewed the scientific literature relevant to the association between

smoking and cardiovascular diseases, non-neoplastic bronchopulmonary diseases, and cancer. Smoking as related to the following diseases and conditions has been reviewed periodically in the reports:

**Pregnancy** (1967, 1969, 1971, 1972, 1973)

**Peptic Ulcer Disease** (1967, 1971, 1972, 1973)

**Noncancerous Oral Disease** (1969)

**Tobacco Amblyopia** (1971)

**Allergy** (1972)

**Public Exposure to Air Pollution From Tobacco Smoke** (1972)

**Harmful Constituents of Cigarette Smoke** (1972)

**Pipe and Cigar Smoking** (1973)

**Exercise Tolerance** (1973)

### *The 1975 Report*

The present document, *The Health Consequences of Smoking, 1975*, begins with an overview of the health consequences of smoking and contains the current data on relationships between smoking and cardiovascular diseases, non-neoplastic bronchopulmonary diseases, and cancer. A fourth chapter, "Involuntary Smoking," reviews the effects to nonsmokers of exposure to smoke-filled environments. Although emphasis is on the latest additions to the literature, where necessary to provide the background or framework, research from earlier years is included.

This report was prepared by the staff of the National Clearinghouse for Smoking and Health in the following way:

1. The Technical Information Center of the Clearinghouse continually monitors and collects the scientific literature on the health consequences of smoking through several established mechanisms:
  - a. An information science corporation is on contract to extract articles on smoking and health from the scientific literature of the world.
  - b. The National Library of Medicine, through the MEDLARS system, provides a monthly listing of articles on smoking and health. Articles not provided by the information science corporation are ordered.

- c. Staff members review current medical literature and identify pertinent articles.
2. The literature was reviewed by the Medical Staff Director who wrote first drafts for this report. These drafts were sent to reviewers for criticism and comment regarding the format, the appropriateness of the articles selected for discussion, and the conclusions. The final drafts of the total report were reviewed by the Director of the National Clearinghouse for Smoking and Health, the Director of the National Cancer Institute, the Director of the National Institute of Environmental Health Sciences, the Director of the National Heart and Lung Institute, and by additional experts both inside and outside the Public Health Service.

## ACKNOWLEDGEMENTS

The National Clearinghouse for Smoking and Health, Daniel Horn, Ph.D., Director, and Charles A. Althafer, Acting Director, are responsible for the preparation of this report. Medical Staff Director for the report was David M. Burns, M.D. Consulting editors were Elvin E. Adams, M.D., Daniel P. Asnes, M.D., John H. Holbrook, M.D., Paul Schneiderman, M.D., and H. Stephen Williams, M.D. Technical Editor was Priscilla B. Holman, and Technical Information Officer responsible for the literature collection was Donald R. Shopland.

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## **INTRODUCTION**

**Overview — The Health Consequences of Smoking\_\_**

## OVERVIEW – HEALTH CONSEQUENCES OF SMOKING

The statement, “*Warning: The Surgeon General Has Determined That Cigarette Smoking Is Dangerous to Your Health*,” has been required by law on cigarette packaging since 1970 as a part of the Public Health Cigarette Smoking Act of 1969. This Act was a response by the U.S. Congress to the scientific information on the health consequences of cigarette smoking summarized in reports then available (the Surgeon General’s Report of 1964 and the subsequent 1967, 1968, and 1969 PHS Health Consequences of Smoking). This Act was passed because a series of important questions concerning cigarette smoking and health had been answered.

The following discussion summarizes the basic questions, the methodology used to determine the answers, and the answers themselves.

The initial question to be answered concerning the health consequences of smoking was “*Are there any harmful health effects of smoking cigarettes?*” The answer to this question was provided in two ways. First, it was demonstrated that some diseases occurred more frequently in smokers than in nonsmokers. Second, a causal relationship was established between smoking and these diseases.

Concern about the possible health effects of smoking started when scientists began looking for an explanation to account for the rapidly increasing death rate from lung cancer. The early retrospective studies showed a link between lung cancer and smoking. The first prospective studies, however, found that only one-eighth of the excess overall mortality found among smokers could be accounted for by lung cancer; the rest was largely due to coronary heart disease, chronic respiratory disease, and other forms of cancer. They also found that the effect on overall mortality was largely confined to cigarette smokers rather than the users of other forms of tobacco.

However, demonstrating an association by statistical probability is not enough to establish the causal nature of a relationship. Determining that the association between smoking and excess death rates is cause and effect was a judgment made after a number of criteria had been met, no one of which by itself is sufficient to make this judgment. These criteria as listed in the Surgeon General’s

Advisory Committee Report (1964) were the **consistency, strength, specificity, temporal relationship, and coherence** of the association.

In addition, convincing theories about the mechanisms whereby smoking contributes to the various diseases responsible for the excess mortality among cigarette smokers were developed from the evidence on the biochemical, cytologic, pathologic, and pathophysiologic effects of cigarette smoking, thereby providing the necessary support for the decision that the relationship was causal.

The most important specific health consequence of cigarette smoking in terms of the number of people affected is the development of premature coronary heart disease (CHD). Both prospective and retrospective studies clearly established that cigarette smokers have a greater risk of death due to CHD and have a higher prevalence of CHD than nonsmokers. Long-term followup of healthy populations has confirmed that a cigarette smoker is more likely to have a myocardial infarction and to die from CHD than a nonsmoker. Cigarette smoking has been shown to be one of the major independent CHD risk factors and to act in combination with other major alterable CHD risk factors (high blood pressure and elevated serum cholesterol). Autopsy studies have shown that persons who smoked cigarettes have more severe coronary atherosclerosis than persons who did not smoke. Physiologic studies and animal experiments have indicated several mechanisms whereby these effects can take place.

A second major health consequence of smoking is the development of cancer in smokers. Cigarette smoking was firmly established as the major risk factor in lung cancer. The risk of developing lung cancer was found to be 10 times greater for cigarette smokers than for nonsmokers. The risk of developing lung cancer increases with the number of cigarettes smoked per day and is greater in cigarette smokers who report inhaling, who started smoking at an early age, or who have smoked for a greater number of years. Smokers of filter cigarettes have been shown to have a lower risk of developing lung cancer than smokers of nonfilter cigarettes, but the risk remains well above that for nonsmokers. The risk of developing cancer of the larynx, pharynx, oral cavity, esophagus, pancreas, and urinary bladder was also found to be significantly higher in cigarette smokers than in nonsmokers. Pipe and cigar smokers were found to have elevated risks for the development of cancer of the oral cavity, pharynx, larynx, and esophagus when compared to nonsmokers. Fewer pipe and cigar smokers than cigarette smokers report that they inhale. As a result lungs of pipe and cigar smokers receive much less

exposure to smoke than the lungs of cigarette smokers. This is probably the primary reason for the lower incidence of cancer of the lung for pipe and cigar smokers compared to cigarette smokers.

Women have had far lower rates of lung cancer than men. This has been attributed to the fact that fewer women than men smoke and the fact that women smokers generally select filter and low tar and nicotine cigarettes. However, the percentage of women smokers in the United States has increased steadily in the last 30 years, and since 1955 the death rates from lung cancer in women have increased proportionately more rapidly than the rates for men, reflecting this increased proportion of women smokers.

The tar from cigarette smoke has been found to induce malignant changes in the skin and respiratory tract of experimental animals, and a number of specific chemical compounds contained in cigarette smoke were established as potent carcinogens or co-carcinogens. Malignant changes including carcinoma *in situ* were found in the larynx and in the sputum exfoliative cytology of experimental animals exposed to cigarette smoke.

Nonmalignant respiratory disease is a third area of smoking-induced morbidity and mortality. Cigarette smokers have been shown to have more frequent minor respiratory infections, miss more days from work due to respiratory illness, and report symptoms of cough and sputum production more frequently than nonsmokers. Retrospective and prospective studies with long-term followup have found that cigarette smoking is the primary factor in the development of chronic bronchitis and emphysema in the United States. Cigarette smokers have also been found to be more likely to have abnormalities of pulmonary function and have higher death rates from respiratory diseases than nonsmokers. Data from autopsy studies have shown that cigarette smokers were more likely to have the macroscopic changes of emphysema, and that these changes are closely related to the number of cigarettes smoked per day. Mucous cell hyperplasia has been found more often in cigarette smokers. Cigarette smoke also inhibits the ciliary motion responsible for cleansing the respiratory tract.

An additional area of health concern has been the effect of cigarette smoking during pregnancy. Mothers who smoke cigarettes during the last two trimesters of their pregnancy have been found to have babies with a lower average birth weight than nonsmoking mothers. In addition cigarette smoking mothers had a higher risk of having a stillborn child, and their infants had higher late fetal and

neonatal death rates. There are some data to show that these risks due to cigarette smoking are even greater in women who have a high risk pregnancy for other reasons. These effects may occur because carbon monoxide passes freely across the placenta and is readily bound by fetal hemoglobin, thereby decreasing the oxygen carrying capacity of fetal blood.

Having established that cigarette smoking is a significant causal factor in a number of serious disease processes, two additional questions became important. They are *"Can the health consequences to the individual be averted by stopping smoking or by changing the cigarette,"* and *"What are the overall public health consequences of cessation and of the changes made in cigarettes?"*

The first question is the simpler of the two to answer. In the individual, cessation of cigarette smoking results in a rapid decline of the carbon monoxide level in the blood over the first 12 hours. Symptoms of cough, sputum production, and shortness of breath usually improve over the next few weeks. A woman who stops smoking by the fourth month of her pregnancy has no increased risk of stillbirth or perinatal death in her infant related to smoking. The deterioration in pulmonary function tests that occurs in some smokers becomes less rapid than that of continuing smokers. The death rates from ischemic heart disease, chronic bronchitis, and emphysema also become less than those of the continuing smoker. The risk of developing cancer of the lung, larynx, and oral cavity declines relative to the continuing smoker in the first few years after cessation and 10 to 15 years after stopping smoking approximates that of nonsmokers. A smoker who switches to filter cigarettes and has smoked them for 10 years or longer has a lower risk of developing lung cancer than a smoker who continues to smoke nonfilter cigarettes. The risk to a filter cigarette smoker, however, still remains well above that of a nonsmoker.

The public health benefits of cessation are more difficult to determine than the effects of cessation on the individual. Just as cause-specific death rates have reflected the effect of cigarette smoking on certain diseases, they should also reflect any substantial benefits to be gained by cessation or reduction in cigarette smoking. Several factors combined to produce a reduction in per capita dosage of tobacco exposure in the United States for the years 1966-1970. First, per capita consumption of cigarettes declined from 4,287 cigarettes per person in 1966 to 3,985 in 1970. Second, during this period there was a slow but significant decrease in the average tar and nicotine content of cigarettes as well as a decrease in the amount of

tobacco contained in the average cigarette. The decline in per capita consumption during those years occurred in the face of a substantial increase in the proportion of young women becoming smokers as compared to women of previous generations and so reflected predominantly a decrease in cigarette consumption by men.

Since 1970, although the per capita consumption of cigarettes has increased, the average levels of tar and nicotine have continued to decline, making it more difficult to predict what has happened to per capita dosage.

Examination of cause-specific death rates for the period of this declining per capita consumption reveals that there was a downturn in the male death rate from ischemic heart disease beginning in 1966 which reversed the upward trend that had occurred over the previous two decades. This decline in the death rate from ischemic heart disease has not occurred in women.

The male death rate from chronic bronchitis has also been declining since 1967, and the male death rate for emphysema has declined since 1968 when it was first recorded as a separate category. Female death rates for these two diseases have not shown these trends.

Despite the impressive coincidences of the decline in death rates among males occurring at the same time that there was a decline in per capita cigarette consumption, it is impossible to be certain of the exact cause of the decline in the death rates. These diseases are influenced by a variety of factors in addition to cigarette smoking such as blood pressure and air pollution. Some of these factors have also been subject to major control efforts which may have contributed to the decline in the death rates. In addition, there have been therapeutic advances in the treatment of these problems which may also have helped lower the death rates.

A decline in male death rates from lung cancer should also follow the decline in per capita consumption. This rate would not be influenced as much by changes in other etiologic factors or changes in therapy because cigarette smoking causes from 85 to 90 percent of all lung cancer and there have been no major improvements in survival due to changes in therapy. With lung cancer, however, two additional considerations must be kept in mind. A decline in death rates from lung cancer would be expected to lag several years behind a decline in per capita consumption. In addition, the decline in consumption and switch to low tar and nicotine cigarettes occurred

predominantly in the younger age groups where death rates from lung cancer are low. For these reasons, it is necessary to look at lung cancer death rates by age group rather than total lung cancer death rates. The lung cancer rates by age groups for 1971 suggest a decline in the lung cancer rates for the younger males (under 45), but the confidence limits on these trends at present remain wide enough that it is impossible to say whether this is a real decline or merely a leveling off. The national health statistics broken down by 5-year age groups are currently available only through 1971. The data by age group from a few more years will be necessary to determine whether the changes in smoking behavior which have taken place have reversed the trend of the preceding 40 years of continually increasing lung cancer rates in men. In 1971, the last year for which detailed mortality statistics are available, the accumulated exposure to cigarettes reached its peak among men born between 1915 and 1919, a group then in their early 50's. Cumulative exposure has continued to decline with each successive 5-year birth cohort born since then. The trends of the last few years offer some hope that the peak of the "lung cancer epidemic," as some have termed this phenomenon, may have been reached with this group and that future years will show a slow but consistent decline.

**CHAPTER 1**  
**Cardiovascular Diseases**



# CHAPTER 1

## Cardiovascular Diseases ---

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## **CORONARY HEART DISEASE (CHD)**

### ***Introduction***

Coronary Heart Disease (CHD) is the most frequent cause of death in the United States and is the most important single cause of excess mortality among cigarette smokers. The evidence relating smoking to CHD has been reviewed in previous reports on the health consequences of smoking (61, 62, 63, 64, 65, 66, 67, 68). The following is a brief summary of the relationships between smoking and CHD presented in these reports.

Cigarette smoking, hypertension, and elevated serum cholesterol are the major alterable risk factors for myocardial infarction and death from CHD. Cigarette smoking acts both independently as a risk factor and synergistically with the other CHD risk factors. The magnitude of the risk increases directly with the amount smoked. The excess risk of CHD among smokers has been demonstrated in some Asian, Black, and Caucasian populations and is proportionately greater for younger men, especially those below age 50. Cessation of cigarette smoking results in a reduced mortality rate from CHD compared with the mortality rate for those who continue to smoke.

Pipe and cigar smokers have a slightly higher risk of death from CHD than nonsmokers, but they incur a much lower risk than cigarette smokers. This has been attributed to the lower levels of inhalation that characterize most pipe and cigar smoking.

Data from autopsy studies have shown coronary atherosclerosis to be more frequent and more extensive in cigarette smokers than in nonsmokers, and experimental work in humans and animals has suggested several mechanisms by which smoking may influence the development of atherosclerosis and CHD. The formation of carboxy-hemoglobin, release of catecholamines, creation of an imbalance between myocardial oxygen supply and demand, and increased platelet adhesiveness leading to thrombus formation have all been demonstrated in smokers and proposed as explanations for the excess CHD mortality and morbidity among smokers.

### *Cigarette Smoking as a Major Risk Factor for Coronary Heart Disease*

The evidence establishing smoking as a major risk factor in CHD has been reviewed in previous reports (61, 62, 63, 64, 65, 66, 67, 68). During the last year new epidemiologic data have been published on the relationship between coronary artery disease and smoking.

Bengtsson (9, 10) studied the smoking habits of women with myocardial infarction (MI) in Goteborg, Sweden. He found that smoking was significantly more common in a group of 46 women (80 percent smokers), ages 50-54, who had a myocardial infarction than in a control group of 578 healthy nonhospitalized women (37.2 percent smokers).

Other investigators examined the effect of cigarette smoking on survival of people with acute myocardial infarction. In a study of 400 patients with documented myocardial infarction who survived to be admitted to a coronary care unit, Helmers (26, 27, 28) found no significant difference between the percentages of smokers and nonsmokers among survivors studied after the first 24 hours, from 2 days until discharge, and from discharge to 3 years. Reynertson and Tzagournis (52), in a 5-year prospective study of 137 patients with documented CHD at age 50 or less, were also unable to find any relationship between CHD mortality rates and smoking habits. Smoking habits after entrance into the study were also considered and again no difference in mortality rates was found.

The Coronary Drug Project (17) found an effect of cigarette smoking on mortality after myocardial infarction. This group studied 2,789 men ages 30-64 years for 3 years after myocardial infarction and found a statistically significant correlation between cigarette smoking determined 3 months after a myocardial infarction and mortality ( $t$ -value of 2.94). None of these studies (17, 26, 27, 28, 52) were able to examine the smoking habits of the group of people who die suddenly as a first manifestation of CHD, and therefore may have excluded that group in which there is the highest excess mortality due to cigarette smoking (31).

Additional data from the Swedish twin study of Friberg, et al. (23) have been reported. They found an excess CHD mortality among smokers in dizygotic twins with different degrees of smoking, but no similar excess in monozygotic twins. Although the numbers were too small to be significant, the authors suggest that this tends to support the theory that both smoking and CHD are constitutionally

determined. These data must be viewed with caution, however, since the difference was demonstrable only in the older age group (born 1901 - 1910). When the younger age group (born 1911 - 1925) was considered, no excess CHD mortality was seen in the dizygotic group but a small excess was noted in the monozygotic group (three CHD deaths in the high smoking group and one in the low smoking group). Also the difference in cigarette consumption between the high and low smoking groups was relatively small (seven cigarettes per day). Consequently, data from this study are not sufficient to warrant the conclusion that both smoking and excess CHD mortality are constitutionally determined rather than smoking being a cause of the excess CHD mortality.

#### *Cigarette Smoking in Relation to Other Risk Factors for Coronary Heart Disease*

Cigarette smoking, elevated serum cholesterol, and elevated blood pressure are generally accepted as the three major modifiable risk factors for CHD. However, there is less agreement concerning other CHD risk factors — obesity, physical inactivity, diabetes mellitus, elevated resting heart rate, psychologic type A behavior, etc. The following studies present recent evidence on the relationships between smoking and hypertension, coffee drinking, and ventricular premature beats.

#### *Hypertension*

Results from several studies have shown that smokers on the average have slightly lower blood pressure than nonsmokers. Some investigators have attributed this finding to the fact that smokers on the average weigh slightly less than nonsmokers. Three current studies (24, 36, 55) discuss this relationship. Gyntelberg and Meyer (24), based on their evaluation of 5,249 men ages 40-59, were of the opinion that lower blood pressure in smokers could not be accounted for by differences in weight, age, or physical fitness. Kesteloot and Van Houte (36), in a study of 42,804 men, performed a multiple regression analysis on age, weight, and height and found that cigarette smokers had lower blood pressure than nonsmokers; however, when they included serum cholesterol values in the analysis, the difference in blood pressure was reduced to approximately 1 mm Hg. Although this difference was statistically significant based on the large population, the actual difference in blood pressure was too small to be of clinical importance.

Seltzer (55) studied 794 men selected for their initial good health and normal blood pressure (below 140 systolic and 90 diastolic) and followed them for changes in cigarette smoking habits, weight, and blood pressure. During the 5-year period of the study 104 men gave up smoking. For every age group except those over 55, there was a significantly greater weight gain (8 lb) among the "quitters" than among the continuing smokers (3.5 lb). Blood pressure increased 4 mm Hg systolic and 2.5 mm Hg diastolic in the quitters with no change in systolic and a slight reduction in diastolic (-1.1 mm Hg) in persons who continued to smoke. In order to examine blood pressure changes in relation to weight change, both continuing smokers and quitters were grouped according to their weight changes during the period of study (Table 1). The most significant finding was an increase in the systolic blood pressure (+1.77 mm Hg) among the quitters even in that group with significant weight loss. In contrast, the continuing smokers with significant weight loss had a decline in systolic blood pressure (-3.28 mm Hg). Diastolic blood pressure in quitters showed an increase with weight gain and no change with weight loss, while continuing smokers showed a decrease in diastolic pressure with weight loss and no change with weight gain. The data on subjects whose blood pressure had increased to hypertensive levels (systolic > 150 and diastolic > 95) were evaluated, and it was found that quitters had a much higher frequency of becoming hypertensive than continuing smokers (Table 2).

Seltzer, in interpreting these data, suggested that cigarette smoking tends to inhibit blood pressure increases, with only minimal pressure rises occurring even in instances of substantial weight gain. When this inhibiting effect of cigarette smoking is removed as in the case of the quitters, sharp rises in blood pressure become evident. He cautioned, however, that the development of hypertension in some quitters may have been responsible for decisions to lose weight and that his data do not allow an evaluation of the degree of blood pressure changes according to how recently cigarettes were given up.

The results of the ischemic heart disease study by Kahn, et al. (34) raise additional questions about Seltzer's data. Kahn followed 10,000 Israeli male civil service employees for 5 years to determine what factors were associated with an increased incidence of hypertension. He presented no data concerning persons who stopped smoking, but he did show that the incidence of hypertension increased with age and that the age-adjusted incidence of hypertension in smokers was over twice that of nonsmokers (76.9/1000 for smokers versus 35.4/1000 for nonsmokers). Seltzer reported no

TABLE 1. — Age-standardized blood pressure changes (mm Hg)<sup>1</sup> at followup for continuing cigarette smokers and quitters according to weight changes

Smoking Class	Weight Change (LB)							
	Significant Wt Loss		No Significant Wt Change		Moderate Wt Gain		Significant Wt Gain	
	No.	lb -25 to -5	No.	lb -4 to +4	No.	lb +5 to +12	No.	lb +13 to +30
<i>Mean systolic BP changes:</i>								
Continuing smokers	32	-4.00	84	-1.52	71	2.85	24	1.50
Quitters	13	1.77	27	2.22	27	4.04	32	3.69
<i>Mean diastolic BP changes:</i>								
Continuing smokers	32	-3.28	84	-2.04	71	0.73	24	-0.04
Quitters	13	-0.31	27	-1.96	27	4.30	32	3.94

<sup>1</sup>Standardized on basis of age distribution of current cigarette smokers.

Source: Seltzer, C.C. (55).

**TABLE 2. — Number of subjects who had developed hypertension at followup for continuing cigarette smokers and quitters**

Blood pressure levels	Continuing cigarette smokers		Quitters	
	Number	Percent	Number	Percent
Systolic blood pressure 150+	6	2.8	9	8.7
Systolic blood pressure 160+	2	0.9	5	4.8
Diastolic blood pressure 95+	3	1.4	5	4.8

Source: Seltzer, C.C. (55).



data on the incidence of hypertension in nonsmokers, and the age distribution for his group of smokers (the original source of the quitters) is heavily weighted toward younger age groups (with only 33 of 214 men age 50 years or over). According to Kahn's data, this age group would be expected to have a lower incidence of hypertension, and, in fact, Seltzer found only small numbers of men who developed hypertension (eight with diastolic hypertension) (Table 2). Making interpretations based on such small numbers is hazardous; for example, the difference between current smokers and quitters in the incidence of diastolic hypertension could have been produced by only three men quitting smoking because they developed hypertension.

### *Coffee Drinking*

The Boston Collaborative Drug Study (12) recently reported a correlation between coffee drinking ( $\geq 6$  cups per day) and myocardial infarction that persisted after controlling for the effect of cigarette smoking. This was a retrospective study of 276 patients with a hospital discharge diagnosis of myocardial infarction and 1,104 age, sex, and hospital-matched controls discharged with other diagnoses. In addition to the usual limitations of retrospective studies, this study has several characteristics that make interpretation difficult. In controlling for the effect of cigarette smoking, the investigators divided the smokers into those who smoked one pack or less per day and those who smoked more than one pack per day. Because cigarette consumption is highly correlated with coffee consumption (29, 39), it can be expected that within such broad smoking categories those who were heavy coffee drinkers tended to be heavier smokers than those who consumed smaller amounts of coffee. It is also possible that the hospitalized controls represented persons who drank less coffee than the general population because of serious chronic illnesses. These characteristics of the study design do not allow firm conclusions to be made concerning the extent to which the relationship between coffee drinking and myocardial infarction is independent of the relationship of both variables to cigarette smoking.

The question of the independent nature of this relationship is also dealt with in a prospective study by Klatsky, et al. (39) of 464 patients with myocardial infarction who previously had had multiphasic health checkups. Both ordinary controls and CHD risk factor-matched controls were drawn from 250,000 people who had undergone the same multiphasic health checkups. The investigators did not find an independent correlation between coffee drinking and myocardial infarction when risk-matched controls were used.

The Framingham Study (18) recently published data on coffee drinking based on a 12-year followup of 5,209 men and women ages 30-62. An increased risk of death from all causes was demonstrated in coffee drinkers, but this relationship was accounted for by the association between coffee consumption and cigarette smoking. No association between coffee drinking and myocardial infarction or between coffee drinking and the development of CHD, stroke, or intermittent claudication was demonstrated. Heyden, et al. (29) also found no relationship between excessive coffee consumption (> 5 cups per day) and atherosclerotic vascular disease.

### ***Ventricular Premature Beats***

Ventricular premature beats have been shown to be a risk factor for sudden death from CHD. Vedin, et al. (69), in a study of 793 men in Goteborg, Sweden, examined the frequency of rhythm and conduction disturbances at rest and during exercise. They found no statistically significant correlation between cigarette smoking habits and the presence of supraventricular or ventricular premature beats at rest or during exercise.

## **CARBON MONOXIDE**

### ***Introduction***

Carbon monoxide has long been recognized as a dangerous gas, but until recently concentrations which produced carboxyhemoglobin levels below 15 to 20 percent were thought to have little effect on humans. Currently there is considerable interest in determining the effect of chronic exposure to low levels of carbon monoxide (65, 66, 67, 68).

Carbon monoxide is present in concentrations of 1 to 5 percent of the gaseous phase of cigarette smoke (11, 45). The concentration varies with temperature of combustion as well as with factors which control the oxygen supply such as the porosity of the paper and packing of the tobacco. The amount of carbon monoxide produced increases as the cigarette burns down. Carboxyhemoglobin levels in smokers vary from 2 to 15 percent depending on the amount smoked, degree of inhalation, and the time elapsed since smoking the last cigarette.

Carbon monoxide, which has 230 times the affinity of oxygen for hemoglobin, impairs oxygen transportation in at least two ways:

First, it competes with oxygen for hemoglobin binding sites. Second, it increases the affinity of the remaining hemoglobin for oxygen, thereby requiring a larger gradient in  $P_{O_2}$  between the blood and tissue to deliver a given amount of oxygen; this increased gradient is usually produced by a lowering of the tissue  $P_{O_2}$ .

Carbon monoxide also binds to other heme-containing pigments, most notably myoglobin, for which it has even a greater affinity than for hemoglobin under conditions of low  $P_{O_2}$ . The significance of this binding is unclear, but may be important in tissues, such as the heart muscle, which have both high oxygen requirements and large amounts of myoglobin.

#### *Sources of Carbon Monoxide Exposure and Human Absorption*

Several researchers (13, 32, 35, 57, 60, 70) have estimated the relative contribution of cigarette smoking and air pollution to the human carbon monoxide burden as measured by carboxyhemoglobin levels (COHb). Kahn, et al. (35), in a study of 16,649 blood donors, determined that smoking was the most important contributing factor, followed by industrial work exposure. Nonsmoking industrial workers had COHb levels of 1.38 percent, and nonsmokers without industrial exposure had levels of .78 percent. Cigarette smokers, on the other hand, had very high levels. Smokers with industrial exposure had levels of 5.01 percent, while smokers without industrial exposure had levels of 4.44 percent (Tables 3 and 4). Stewart, et al. (57) found similar results in a nationwide survey of blood donors and noted marked variation in mean COHb levels in residents of different cities measured at different times of the year (Table 5). However, in all areas, smokers still had COHb levels two to three times higher than nonsmokers and had increasing COHb levels with increasing level of cigarette consumption (Table 6). Similar findings were reported by Torbati, et al (60) in a study of 500 male Israeli blood donors.

Nonsmoking workers exposed to automobile exhaust – London taxi drivers (32) and garage and service station operators (13) – have higher baseline levels of carboxyhemoglobin than nonsmokers of the general population. But even in these high exposure occupations smokers have markedly higher COHb levels (8.1 and 10.8 percent) than nonsmokers (6.3 and 5.5 percent). An extreme is represented by New York City tunnel workers who are exposed to an average of 63 ppm CO with peak exposure levels as high as 217 ppm CO; cigarette smokers still maintained much higher COHb levels (5.01 percent) than nonsmokers (2.93 percent) (8).

**TABLE 3. – Mean percent of carboxyhemoglobin saturation in smokers and nonsmokers by sex and race**

	Total Sample		Nonsmokers		Smokers <sup>1</sup>	
	No.	$\bar{X} \pm S_{\bar{X}}$	No.	$\bar{X} \pm S_{\bar{X}}$	No.	$\bar{X} \pm S_{\bar{X}}$
Total Sample	16,649	$2.30 \pm 0.02$	10,157	$0.85 \pm 0.01$	6,492	$4.58 \pm 0.03$
Male	10,542	$2.66 \pm 0.03$	5,888	$1.00 \pm 0.01$	4,654	$4.76 \pm 0.04$
Female	6,107	$1.68 \pm 0.03$	4,269	$0.64 \pm 0.01$	1,838	$4.10 \pm 0.06$
White	15,167	$2.28 \pm 0.02$	9,474	$0.85 \pm 0.01$	5,693	$4.66 \pm 0.04$
Male	9,669	$2.65 \pm 0.03$	5,508	$1.00 \pm 0.01$	4,161	$4.83 \pm 0.04$
Female	5,498	$1.63 \pm 0.03$	3,966	$0.64 \pm 0.01$	1,532	$4.19 \pm 0.06$
Black	1,429	$2.59 \pm 0.06$	641	$0.86 \pm 0.03$	788	$4.00 \pm 0.08$
Male	829	$2.91 \pm 0.10$	347	$1.07 \pm 0.05$	482	$4.24 \pm 0.10$
Female	600	$2.15 \pm 0.09$	294	$0.62 \pm 0.04$	306	$3.63 \pm 0.12$

<sup>1</sup>Smokers are defined as those who smoked on the day of giving blood.

NOTE. –  $\bar{X}$  = mean percent;  $S_{\bar{X}}$  = standard error of mean percent.

Source: Kahn, A., et al. (35).

**TABLE 4. – Mean percent of carboxyhemoglobin saturation in smokers  
and nonsmokers by employment status**

	Nonsmokers		Smokers <sup>1</sup>	
	No.	$\bar{X} \pm S_{\bar{X}}$	No.	$\bar{X} \pm S_{\bar{X}}$
Persons employed	8,478	$0.89 \pm 0.01$	5,962	$4.61 \pm 0.03$
Classed as industrial workers <sup>1</sup>	1,523	$1.38 \pm 0.04$	1,738	$5.01 \pm 0.06$
Classed as workers other than industrial	6,955	$0.78 \pm 0.01$	4,224	$4.44 \pm 0.04$
Persons not employed	1,678	$0.63 \pm 0.02$	531	$4.24 \pm 0.11$

<sup>1</sup>Industrial workers are employed in either durable or nondurable goods manufacturing (craftsmen, operatives, or laborers). Smokers are defined as those who smoked on the day of giving blood.

NOTE. –  $\bar{X}$  = mean percent;  $S_{\bar{X}}$  = standard error of mean percent.

Source: Kahn, A., et al. (35).

**TABLE 5. – Median percent carboxyhemoglobin (COHb) saturation and 90 percent range for smokers and nonsmokers by location**

Location	Cigarette Smokers		Nonsmokers	
	Median	Range	Median	Range
Anchorage	4.7	0.9 – 9.5	1.5	0.6 – 3.2
Chicago	5.8	2.0 – 9.9	1.7	1.0 – 3.2
Denver	5.5	2.0 – 9.8	2.0	0.9 – 3.7
Detroit	5.6	1.6 – 10.4	1.6	0.7 – 2.7
Honolulu	4.9	1.6 – 9.0	1.4	0.7 – 2.5
Houston	3.2	1.0 – 7.8	1.2	0.6 – 3.5
Los Angeles	6.2	2.0 – 10.3	1.8	1.0 – 3.0
Miami	5.0	1.2 – 9.7	1.2	0.4 – 3.0
Milwaukee	4.2	1.0 – 8.9	1.2	0.5 – 2.5
New Orleans	5.5	2.0 – 9.6	1.6	1.0 – 3.0
New York	4.8	1.2 – 9.1	1.2	0.6 – 2.5
Phoenix	4.1	0.9 – 8.7	1.2	0.5 – 2.5
St. Louis	5.1	1.7 – 9.2	1.4	0.9 – 2.1
Salt Lake City	5.1	1.5 – 9.5	1.2	0.6 – 2.5
San Francisco	5.4	1.6 – 9.8	1.5	0.8 – 2.7
Seattle	5.7	1.7 – 9.6	1.5	0.8 – 2.7
Vermont,				
New Hampshire	4.8	1.4 – 9.0	1.2	0.8 – 2.1
Washington, DC	4.9	1.2 – 8.4	1.2	0.6 – 2.5

Source: Stewart, R.D., et al. (57).

**TABLE 6. – Mean percent carboxyhemoglobin (COHb) saturation in cigarette smokers 1 hour after last cigarette**

Location	Nonsmoker	Packs of Cigarettes Smoked Per day				
		< ½	½-1	1	1½	2
Milwaukee	1.3	3.0	4.2	5.3	6.2	4.7
New Hampshire, Vermont	1.4	3.3	4.4	5.7	6.7	5.3
New York City	1.4	3.1	4.3	4.7	5.8	6.3
Washington, DC	1.4	3.8	4.6	5.2	5.8	6.6
Los Angeles	2.0	4.0	5.2	6.0	7.4	7.5
Chicago	2.0	4.8	5.4	6.3	7.1	7.7

Source: Stewart, R.D., et al. (57).

Studies on the CO burden of each cigarette have determined the body burden of CO per cigarette to be 7.10-8.66 ml (40), and the increase in COHb level produced by smoking one cigarette to be .94 to 1.6 percent after 12 hours of abstinence (40, 53). The half-life for the washout of CO in healthy college smokers (40) was calculated to be from 3 to 5 hours.

### *Effects on Healthy Individuals*

Several studies have been published on the effects of carbon monoxide on healthy individuals. Small doses of CO (COHb levels 2.4-5.4 percent) were found to have no effect on heart rate (56). Raven, et al. (51), in a study of young men exposed during exercise on a treadmill to 50 ppm CO (COHb levels 2.5 percent in nonsmokers and 4.1 in smokers), found no decrease in maximum aerobic capacity when the subjects were tested at 25° C. In a similar experiment conducted at 35° C by the same researchers (20), there was a decrease in maximum aerobic capacity in nonsmokers exposed to 50 ppm CO, but not in smokers despite an increase in the carboxyhemoglobin levels of 1.5 percent in both groups. They postulated a possible physiologic adaptation of smokers to carbon monoxide. Ekblom and Huot (22) studied five young men who inhaled CO to reach given COHb levels. They reported that as COHb levels increased, there was a decrease in maximal oxygen uptake and lower heart rates at maximal treadmill exercise.

Sagone, et al. (54), in a study of 9 cigarette smokers and 18 nonsmokers ages 20-32, showed significantly higher values for COHb, red cell mass, hemoglobin, and hematocrit in the smokers. Levels of 2,3 DPG were unaltered while oxyhemoglobin affinity P50 and ATP levels were significantly lower in the smokers. The three smokers with highest red cell mass had normal arterial blood gases and one smoker had very high values of red cell mass which returned to normal after he stopped smoking. The authors interpret these data as evidence of tissue hypoxia.

Millar and Gregory (43), in a study of both fresh heparinized blood and ACD-stored blood from a blood bank, showed a reduction in the oxygen carrying capacity of up to 10 percent in the blood of cigarette smokers; this reduction persisted for the full 21-day storage life of blood bank blood.

Cole, et al. (16), in a study of pregnant women, found COHb levels in the fetus to be 1.8 times as great as those in the



simultaneously measured blood of the mother. Fetal blood was exposed to carbon monoxide in vitro, and fetal hemoglobin was found to have a shift of the oxyhemoglobin disassociation curve to the left as occurs with adult hemoglobin. The higher fetal COHb levels were attributed to the lower fetal  $P_{O_2}$  and a resultant decrease in the ability of oxygen to compete for the fetal hemoglobin. It was felt by the authors that the high COHb levels may be responsible for the lower birth weight of infants born to mothers who smoke.

#### *Effects on Persons with Atherosclerotic Cardiovascular Disease*

Aronow and Isbell (5) and Anderson, et al. (1) have shown a decrease in the mean duration of exercise before the onset of pain in patients with angina pectoris exposed to low levels of carbon monoxide (50 and 100 ppm). Carboxyhemoglobin levels were significantly elevated (2.9 percent after 50 ppm; 4.5 percent after 100 ppm) and the systolic blood pressure, heart rate, and product of systolic blood pressure times heart rate (a measure of cardiac work) were all significantly lower at onset of angina pectoris.

In a continuation of this work, Aronow, et al. (2, 3) studied eight patients during two separate cardiac catheterizations, one during which each patient smoked three cigarettes and one during which each patient inhaled carbon monoxide until the maximal coronary sinus COHb level equalled that produced by smoking during the first catheterization. All eight had angiographically demonstrated CHD (> 75 percent obstruction of at least one coronary artery). Smoking increased the systolic and diastolic blood pressure, heart rate, left ventricular end-diastolic pressure (LVEDP), and coronary sinus, arterial, and venous CO levels. No changes were noted in left ventricular contractility (dp/dt), aortic systolic ejection period, or cardiac index, and decreases were found in stroke index and coronary sinus, arterial, and venous  $P_{O_2}$ . When carbon monoxide was inhaled, increased LVEDP and coronary sinus, arterial, and venous CO levels were noted; there were no changes in systolic and diastolic blood pressure, heart rate, or systolic ejection period; and decreases in left ventricular dp/dt, stroke index, cardiac index and coronary sinus, arterial, and venous  $P_{O_2}$  were found. These data suggest that carbon monoxide has a negative inotropic effect on myocardial tissue resulting in the decrease in contractility (dp/dt) and stroke index. When the positive effect of nicotine on contractility and heart rate is added by cigarette smoking, the net effect is increased cardiac work for the same cardiac output. In the heart with

coronary artery disease there is a greatly restricted capacity to increase blood flow in response to this increase in cardiac work. The result is early cardiac decompensation manifested by elevation in LVEDP and angina pectoris.

Aronow, et al. have also shown decreased exercise time prior to onset of angina pectoris in persons exercised after riding for 90 minutes on the Los Angeles Freeway (4). In a related study, they demonstrated a decrease in exercise time before claudication in a group of patients with intermittent claudication who were exposed to 50 ppm CO (6).

### *Studies on the Pathogenesis of Cardiovascular Disease*

In a review of some of their work on carbon monoxide, Astrup and Kjeldsen (7) noted that in cholesterol-fed rabbits exposed to 170 ppm carbon monoxide for 7 weeks (COHb 16 percent) and then to 340 ppm for 2 weeks, the cholesterol content of the aorta was 2.5 times higher than that of cholesterol-fed, air breathing controls. Groups of cholesterol-fed rabbits intermittently exposed to carbon monoxide for 12 or 4 hours per day produced three- to fivefold increases in the cholesterol content of their aortas. Cholesterol-fed rabbits made hypoxic at 10 and 16 percent oxygen had 3 to 3.5 times the aortic cholesterol content, while those exposed to 26 and 28 percent oxygen had a considerable decrease in cholesterol accumulation.

Theodore, et al. (58) studied the aortas of monkeys, baboons, dogs, rats, and mice fed a normal diet but exposed to very high levels of CO (COHb levels 33 percent) and found no atheromatous changes in their aortas.

Further work by Astrup and Kjeldsen (38) revealed that in rabbits fed normal diets but exposed to 180 ppm carbon monoxide for 2 weeks, there were local areas in their hearts of partial or total necrosis of myofibrils; in the arteries there was endothelial swelling, formation of subendothelial edema, and degeneration of the myocytes. When the aortas of these rabbits were examined (37), the luminal coats showed pronounced changes characterized by severe edematous reaction with extensive swelling and formation of subendothelial blisters and plaques. The authors postulate that carbon monoxide increases endothelial permeability to albumin which results in formation of edema leading to changes indistinguishable from early atherosclerosis.

Evidence that this mechanism may occur in humans is provided by the findings of Parving (50) who showed an increased transcapillary escape rate for  $^{131}\text{I}$ -labeled albumin in humans exposed to .43 percent CO (COHb 20 percent) for 3 to 5 hours, but not in those made hypoxic to an altitude of 4300 meters (hemoglobin 75 percent saturated).

By exposing rabbits to different concentrations of carbon monoxide (50, 100, and 180 ppm) for varying periods (.5, 2, 4, 8, 24, and 48 hours), Thomsen and Kjeldsen (59) were able to show a threshold of 100 ppm of CO for myocardial damage. The demonstration of damage at this level of CO (COHb 8-10 percent) is possibly explained by the ratio of carboxymyoglobin to carboxyhemoglobin which is about 3 to 1 in myocardium at ambient  $\text{Po}_2$ . Thus, a COHb level of 10 percent would be accompanied by a carboxymyoglobin level of 30 percent in heart muscle. This ratio is even greater under hypoxic conditions with a ratio of 6 to 1 when the arterial  $\text{Po}_2$  is below 40 mm Hg (15).

### *Nicotine*

In a study of the effects of smoking cigarettes with low and high nicotine content, Hill and Wynder (30) noted increasing serum epinephrine levels with increasing nicotine content of the smoke, but serum norepinephrine levels were unchanged. However, increasing serum epinephrine levels with increasing number of low nicotine content cigarettes smoked were also noted.

### *Acrolein*

Egle and Hudgins (21) did inhalation studies with acrolein on rats. Inhalation of this aldehyde at concentrations below those encountered in cigarette smoke resulted in a significant increase in blood pressure and heart rate in rats.

## **CEREBROVASCULAR DISEASE**

There has been conflicting evidence on whether there is an increased risk of cerebrovascular disease due to smoking (61, 62, 63, 64, 65, 66, 67, 68). A prospective study by Paffenbarger, et al. (48) of 3,991 longshoremen followed for 18 years showed no correlation between fatal strokes and smoking. However, both the Dorn study of

U.S. veterans (33) and Hammond's study of one million men and women (25) showed a small but significant increase in the death rates from cerebrovascular disease among cigarette smokers. The Framingham 18-year followup of men ages 45 to 54 (42) and Paffenbarger's study of men who entered Harvard between 1916 and 1940 (49) also showed an excess risk of cerebrovascular disease associated with cigarette smoking.

Two recent studies provided more data on this topic. Ostfeld, et al. (46, 47), in a study of 2,748 people ages 65-74 receiving old age assistance in Cook County, Illinois, were unable to find any relation between cigarette smoking habits at the start of the study and incidence of new strokes or prevalence of transient ischemic attacks. Nomura, et al. (44), in a study of the population of Washington County, Maryland, ages 25 and older, were unable to find any relation between cigarette smoking and either mortality or morbidity from stroke. Nomura noted that "in atherosclerotic strokes the Framingham study and Paffenbarger's investigation of former college students included a great percentage of stroke cases under the age of 55. Because these two studies found an association between cigarette smoking and atherosclerotic strokes and the present study did not, it may be that the association is age-dependent."

Hammond (25) provides some data which may clarify this relationship. Analysis of his data shows that the difference between cerebrovascular death rates in cigarette smokers and nonsmokers increases as persons get older except in males ages 75-84 (Table 7), indicating that the excess death rates associated with cigarette smoking increase with advancing age. The ratio of the death rates for smokers and nonsmokers (mortality ratio), however, decreases with age, reflecting the fact that cerebrovascular disease death rates attributable to other causes increase with age more rapidly than death rates attributable to smoking. Cigarette smoking may well be a risk factor for stroke at all ages, but other causes of strokes become proportionally so important in older age groups that in studies not based on very large populations the risk due to cigarette smoking is masked by the large total number of strokes due to other causes.

**TABLE 7. — Age-standardized deaths rates and mortality ratios for cerebral vascular lesions for men and women by type of smoking (lifetime history) and age at start of study**

Type of Smoking	Age Groups			
	45–54	55–64	65–74	75–84
<b>CVL Death Rates per 100,000 Person-Years</b>				
<b>Men</b>				
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
<b>Women</b>				
Never smoked regularly	18	57	228	1,082
Cigarette	38	88	315	1,277
Total	25	64	238	1,091
<b>CVL Mortality Ratios</b>				
<b>Men</b>				
Never smoked regularly	1.00	1.00	1.00	1.00
Pipe, cigar	0.89	1.09	1.06	1.01
Cigarette and other	1.00	1.40	1.03	0.73
Cigarette only	1.50	1.41	1.37	0.86
<b>Women</b>				
Never smoked regularly	1.00	1.00	1.00	1.00
Cigarette	2.11	1.54	1.38	1.18

NOTE. — CVL = Cerebral vascular lesions.

Source: Hammond, E.C. (25).

## EFFECTS OF SMOKING ON THE COAGULATION SYSTEM

Several studies have contributed to an understanding of the role of smoking in thrombogenesis. Levine (41), in a controlled double blind study, showed that smoking a single cigarette increased the platelet's response to a standard aggregating stimulus (ADP). This phenomenon did not occur when lettuce leaf cigarettes were smoked and was independent of a rise in free fatty acids in the plasma. The author postulates that this may be due to increasing epinephrine levels.

These data may have relevance for two other studies. In the clinical trial of the possible prevention of heart attack by hyperlipidemic drugs in Newcastle, England, (19) it was found that cigarette smokers were at increased risk of sudden death. This increased risk was not present in smokers treated with clofibrate. However, the researchers were unable to relate this reduction in risk to any effect of clofibrate on serum lipids. Recently Carvalho, et al. (14) evaluated 29 patients with familial hyperbetalipoproteinemia and noted that their platelets had an increased sensitivity to aggregating stimuli (ADP). Treatment with clofibrate returned the ADP sensitivity to normal without significantly altering serum lipids. This demonstrated effect of clofibrate may provide some insight into the Newcastle study. The reduction in the excess risk of sudden death could be due to a clofibrate induced reversal of increased sensitivity to aggregating stimuli produced by smoking.

## **SUMMARY OF RECENT CARDIOVASCULAR FINDINGS**

1. Data from one recent incidence study suggest that cigarette smokers are more likely to develop hypertension than are nonsmokers. There is some evidence that suggests that stopping smoking may be accompanied by a rise in blood pressure.

2. Cigarette smoking has been shown to be the major source of elevated carboxyhemoglobin levels, with occupational exposure and air pollution being far less important in most circumstances. Carboxyhemoglobin levels in cigarette smokers are two to three times the levels in nonsmokers and increase with the amounts smoked.

3. Elevated carboxyhemoglobin levels have been shown to decrease maximal oxygen uptake in healthy people as well as to decrease the exercise tolerance of persons with angina pectoris and intermittent claudication. The carboxyhemoglobin levels at which these effects take place are well within the range produced by cigarette smoking.

4. Carbon monoxide at levels of exposure commonly reached by cigarette smokers has been shown to decrease cardiac contractility in persons with coronary heart disease.

5. Carbon monoxide has been shown to produce changes like those of early atherosclerosis in the aortas of rabbits.

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**CHAPTER 2**  
**Cancer**

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## INTRODUCTION

The major relationships between smoking and various cancers have been documented in previous reports on the health consequences of smoking (18, 19, 20, 21, 22, 23, 24, 25). Based on evaluations of detailed epidemiologic, clinical, autopsy, and experimental data accumulated over the last 30 years, cigarette smoking has been clearly identified as a causative factor for lung cancer. The risk of developing lung cancer increases directly with increasing cigarette smoke exposure as measured by number of cigarettes smoked per day, total lifetime number of cigarettes smoked, number of years of smoking, age at initiation of smoking, and depth of inhalation. Lung cancer death rates for women are lower than for men but have increased dramatically over the last 15 years coincident with the increasing number of women smokers. This increase has occurred in spite of the fact that women smokers use fewer cigarettes per day, more frequently choose cigarettes with filter tips and low tar and nicotine delivery, and tend to inhale less than men. A person who stops smoking has a decreased risk of developing lung cancer compared to the continuing smoker, but the risk remains greater than the nonsmoker's for as long as 10 to 15 years after the person stops smoking.

Cigarette smoking is a significant etiologic factor in the development of cancer of the larynx, oral cavity, pharynx, esophagus, and urinary bladder and is associated with cancer of the pancreas.

Certain occupational exposures have been found to be associated with an increased risk of dying from lung cancer. Cigarette smoking interacts with these exposures to produce a greater risk of developing lung cancer than from occupational exposure alone. Uranium mining and the asbestos industries are occupations which have only slightly increased lung cancer rates for nonsmokers but dramatically elevated rates for cigarette smokers.

Pipe and cigar smokers experience mortality rates from cancer of the oral cavity, larynx, pharynx, and esophagus approximately equal to those of cigarette smokers. Their risk of developing cancer of the lung is lower than the risk of cigarette smokers, but it is significantly above that of nonsmokers. This is probably due to the



fact that pipe, cigar, and cigarette smokers experience similar smoke exposure of the upper respiratory tract, while cigarette smokers (due to their greater tendency to inhale) have a greater exposure of their lungs to smoke than pipe or cigar smokers.

The bronchial epithelium of smokers often shows premalignant changes such as squamous metaplasia, atypical squamous metaplasia, and carcinoma *in situ*. The pathogenesis of these changes is related to the various carcinogenic and co-carcinogenic substances in cigarette smoke; the exact mechanism of these carcinogens remains under investigation.

## **LUNG CANCER**

### ***Epidemiologic Studies***

Harris (3) has reviewed the reports of lung cancer in nonsmokers and compared them to a representative hospital series and has shown marked differences in the pathological types between the two groups (Table 1). When only nonsmokers are examined, the excess of squamous and oat cell carcinoma in men compared to women is not observed. Adenocarcinoma is by far the most common type of lung cancer in nonsmokers while squamous cell is by far the most common when smokers are included. The strength of the relationship between smoking and the development of lung cancer differs markedly with the type of lung tumor. Squamous and oat cell carcinoma are very closely related to smoking behavior while, according to this study, bronchiolar carcinoma shows no excess risk attributable to smoking. Harris also presented the percentages of different histologic types of cancer found in several industrial exposures (Table 2); these percent distribution patterns resembled those found in smokers far more closely than those found in nonsmokers.

Wynder, et al. (26), in a retrospective study of 350 lung cancer patients and hospitalized controls, noted that the relative risk of developing lung cancer was far less in those smokers who had smoked filter cigarettes for more than 10 years than in smokers of plain cigarettes (26.8 and 46.2, respectively). Even with smokers of filter cigarettes, the risk increased with increasing number of cigarettes smoked and was significantly greater than the risk of nonsmokers.

### ***Smoking and Air Pollution***

Because of the magnitude of the association between smoking and the development of epidermoid lung cancer, it is difficult to

**TABLE 1. – Distribution by type of lung cancers in a composite series of nonsmokers and a representative hospital series**

Type of cancer	Distribution (Percent)			
	Nonsmokers		All Patients	
	Men	Women	Men	Women
Squamous cell carcinoma	14	12	47	22
Oat cell carcinoma	4	4	17	11
Bronchiolar carcinoma	—	5	8	23
Adenocarcinoma	57	54	10	20
Large cell anaplastic carcinoma	8	8	17	19
Carcinoid	14	16	0.6	4
Other specific types	—	< 1	1	2
Undifferentiated <sup>1</sup>	4	2	—	—
Total number of cases	51	274	1,903	315

<sup>1</sup>Includes oat cell carcinoma and large cell anaplastic carcinoma.  
Source: Harris, C.C. (3).

TABLE 2. – *Distribution by type of lung cancer in populations with specific occupational exposures*

Type of cancer	Distribution (%) in populations with exposure to—				
	Arsenic	Nickel	Chromium	Hematite	Asbestos
Squamous cell carcinoma	40	57	48	33	44
Oat cell carcinoma	13	43	16	60	6
Adenocarcinoma	7	—	24	—	25
Oat cell or anaplastic carcinoma	40	—	—	—	24
Anaplastic	—	—	12	7	1

Source: Harris, C.C. (3).

evaluate the effects of other possible causes of lung cancer such as air pollution. Higgins (4) recently analyzed respiratory cancer mortality in Great Britain and the United States. In the United States, although the age-specific death rates for males continued to increase, the rate of increase was not as great as in the past. Female lung cancer mortality rates, by contrast, have increased steadily since about 1955. If these increases continue, the American Cancer Society estimates that lung cancer among women will move from fourth to third place in 1975 as the site responsible for the greatest number of deaths due to cancer among women (1). In England and Wales, Higgins noted that between 1940 and 1969 lung cancer rates for men declined in the age group under 55 and increased only in men over 65. After adjusting for cigarette smoking, an independent effect of air pollution was sought. It was found that the lung cancer death rates for men ages 25-64 in greater London decreased more than the rates in the rest of the country; he attributed this decrease to the greater decline in smoke pollution in London than elsewhere.

### *Exfoliative Cytology*

Microscopic examination of respiratory epithelial cells shed into the sputum has become a useful aid in the diagnosis of lung cancer and has been employed in many lung cancer screening programs for selected high risk groups. Saccomanno, et al. (11) have conducted periodic cytologic examinations of the sputum of uranium miners and a group of nonmining controls. Many of these individuals developed abnormal squamous cell metaplasia that progressed in several cases to become invasive carcinoma. Both cigarette smoking and radiation exposure from uranium mining were associated with an increased prevalence of these cytologic changes. Of the two factors, cigarette smoking was noted to be the more important (in both miners and nonminers) for the development of atypia and carcinoma *in situ*. Neither cigarette smoking nor uranium mining could be correlated with the length of time it took for these changes to progress from one pathologic stage to the next.

Schreiber, et al. (15) studied exfoliative cytology of the lungs of hamsters treated with intratracheal injection of the carcinogen benzo(a)pyrene. They noted progression from mild atypia to squamous metaplasia, to moderate and marked atypia, to changes indicative of cancer. These cytologic changes in animals exposed to carcinogens are comparable to those found in humans who smoke cigarettes.

## EXPERIMENTAL CARCINOGENICITY

### *Carcinogens in Cigarette Smoke*

A great deal of effort has been expended to identify those substances in cigarette smoke that cause malignant changes. The hope is that, if these carcinogenic substances can be identified and removed from cigarette smoke, the risk of developing lung cancer as a result of smoking can be reduced. Carcinogenic substances which act as tumor initiators, accelerators, and promoters in experimental animal systems have been identified in cigarette smoke.

Hoffman and Wynder (6) conducted an extensive analysis of the tumorigenicity of tobacco smoke. Using the gas phase of cigarette smoke, they identified certain known carcinogens but were unable to induce carcinoma in the respiratory tract of experimental animals. They interpreted these results as indicating that the levels of carcinogens present in the gas phase alone are below the concentrations necessary for tumor activity.

In the same study, Hoffmann and Wynder examined the particulate phase of tobacco and identified several carcinogens. The majority of tumor initiators in the particulate phase were polynuclear aromatic hydrocarbons and alkylated polynuclear aromatic hydrocarbons. They found that a significant inhibition of pyrosynthesis of these substances leads to a significant reduction of the tumorigenicity of tobacco smoke. They also identified several tumor accelerators – substances which accelerate the carcinogenicity and tumor initiating activity of the polycyclic aromatic hydrocarbons. The tumor accelerators found were *trans*-4, 4'-dichlorostilbene, *N*-alkyl indoles, and *N*-alkyl carbazoles. They also reported that the tumor promoters in cigarette smoke occur in the acidic portion of the particulate matter but did not further characterize them.

Hoffmann, et al. (5) reported identifying the nitrosamine, *N*'-nitrosonornicotine, in concentrations of 1.9 to 6.6 micrograms per gram in unburned tobacco and levels of 88.6  $\mu\text{g/g}$  in one sample of finely cut chewing tobacco. This is one of the highest concentrations of an environmental nitrosamine (a family of compounds containing several organic carcinogens) yet identified; concentrations in food and drink rarely exceed 0.1  $\mu\text{g/g}$ . This substance is readily extractable from tobacco by water and so would be present in high concentrations in the saliva of persons who chew

tobacco. As yet, *N'*-nitrosonornicotine has not been established as carcinogenic, and even the known carcinogenic nitrosamines are not felt to act topically.

### *Asbestos*

The combination of cigarette smoking and asbestos exposure has been shown to result in a particularly high risk of developing lung cancer. Selikoff, et al. (16) have shown that asbestos workers who smoke have 90 times greater risk of developing lung cancer than nonsmoking, nonexposed people. Shabad, et al. (17) recently studied the possible causes of the synergistic effect of cigarette smoke and asbestos. They studied the carcinogenic activity of different types of asbestos in the U.S.S.R. and noted that all samples of chrysotile asbestos had traces of benzo(a)pyrene (a polycyclic aromatic hydrocarbon carcinogen found in cigarette smoke). In addition, they noted that chrysotile asbestos had a high adsorption activity for benzo(a)pyrene. This was not found in the other types of asbestos tested (anthophyllite and magnesiarfvedsonite). In these animal studies, 20 percent of the rats exposed to chrysotile asbestos developed precancerous lesions; inhalation of chrysotile plus benzo(a)pyrene or of chrysotile plus cigarette smoke increased the frequency of the lesions to 57 and 38 percent, respectively. The synergism between asbestos and smoking may be the result of the adsorption of carcinogens onto asbestos, therefore prolonging their retention in the lung.

### *Infection and Carcinogenicity*

There has been some discussion concerning the association between lung cancer and chronic bronchitis. Both diseases can be caused by cigarette smoking; however, chronic bronchitis may also influence the development of lung cancer by some independent mechanism. Schreiber, et al. (14) administered *N*-nitrosoheptamethyleneimine to germfree rats, specific-pathogen-free rats, and rats with chronic murine pneumonia. The incidence of lung neoplasms was 17 percent in germfree males, 37 percent in specific pathogen-free males, and 83 percent in infected males. An incidence of 90 to 100 percent occurred among females in all three experimental groups. They concluded that chronic respiratory infection may enhance the neoplastic response of the lungs to a systemic carcinogen.

## OTHER CANCERS

### *Oral and Laryngeal Cancer*

Schottenfeld, et al. (13) have studied the role of smoking on the development of multiple primary cancers of the upper digestive system, larynx, and lung. They followed 733 patients surviving a first primary epidermoid cancer of the oral cavity, pharynx, or larynx for 5 years. The average annual incidence for a second primary was higher in men (18.2/1000) than in women (15.4/1000). Both men and women who developed a second primary tumor had heavier tobacco exposure prior to their first cancer than those who did not develop a second malignancy. The authors were unable to show a significant relationship between smoking habits after removal of the first primary and development of a second primary. They postulate that this failure to show an association is due to the long induction period between presence of a carcinogen and occurrence of the cancer, and they expect that a relationship, if present, may become apparent after 7 or 8 years of followup.

### *Genitourinary Cancer*

Schmauz and Cole (12) studied 43 persons with cancer of the renal pelvis or ureter and noted that smoking was only a risk factor at very high levels of consumption (over 2½ packs per day), despite its being related to cancer of the bladder at all levels of smoking. They postulate that, due to the rapid transit of urine through the renal pelvis and ureter, very high levels of exposure are required to have any effect whereas the bladder stores urine for some time and even small amounts of carcinogens in the urine may be sufficient to influence the bladder epithelium.

### *Nasopharyngeal Cancer*

Lin, et al. (10), in a retrospective study of nasopharyngeal cancer in Taiwan using neighborhood controls, found smoking to be significantly associated with the development of nasopharyngeal carcinoma. A person smoking over 20 cigarettes per day had twice the risk of a nonsmoker of developing nasopharyngeal cancer.

## ARYL HYDROCARBON HYDROXYLASE (AHH)

Due to the great variation in the amount of smoking exposure before the development of lung cancer, attempts have been made to

identify groups of people who may have a greater sensitivity to the carcinogenic effect of cigarette smoke. Interest has developed in the possibility that aryl hydrocarbon hydroxylase (AHH) may be a genetically determined enzyme that mediates such increased susceptibility to certain environmental carcinogens.

AHH is an enzyme system which metabolizes polycyclic aromatic hydrocarbons; some of the resulting metabolites are carcinogenic. It has been postulated that persons with high levels of this enzyme may be at greater risk of developing cancer from exposure to the polycyclic hydrocarbons in cigarette smoke than those with low levels.

The amount of AHH produced in response to an inducing stimulus can be used to separate a population into three groups (those capable of being induced to produce high, medium, and low levels of AHH). Kellerman, et al. (8) studied the induction of AHH activity in 353 healthy subjects (67 families with 165 children). They felt that the enzyme was controlled by a single gene locus with two alleles (one able to be induced to produce high AHH levels with a gene frequency of .283 and one, to produce low levels with a gene frequency of .717). All six possible crossmatings were found in the families studied, and no deviations from the expected phenotypes were found in the children.

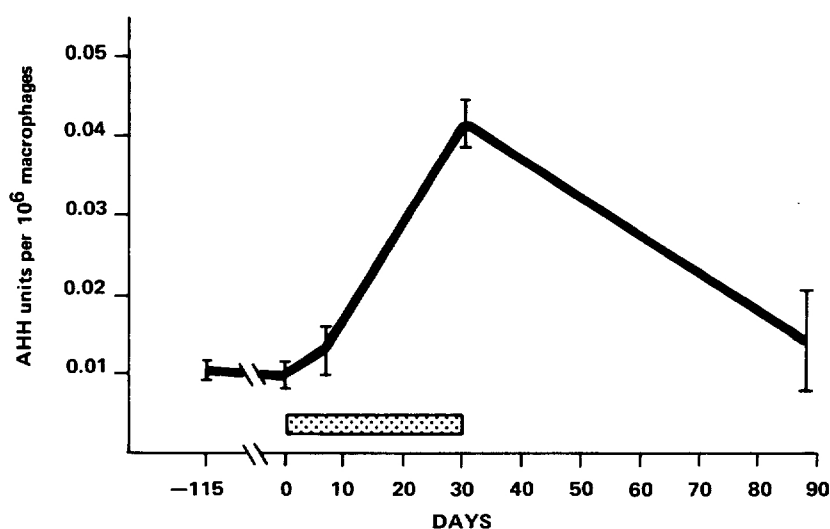
Cantrell, et al. (2), studied 19 healthy volunteers and found that cigarette smokers had higher levels of AHH in their pulmonary alveolar macrophages than nonsmokers. In one subject they showed an increase in AHH activity starting 1 week after he began to smoke 10 to 15 cigarettes per day (2, Fig. 1). Holt and Keast (7) also showed increased levels of AHH activity in homogenates of lung tissue from mice exposed to cigarette smoke.

Kellermann (9) also studied the inducibility of AHH in the lymphocytes of 50 patients with bronchogenic carcinoma and compared them to a healthy white population and to a group of patients with nonrespiratory malignancies (Table 3). They found that lung cancer patients had a statistically significant, higher percentage of persons homozygous for the high allele, i.e., able to be induced to high AHH levels, than either the healthy or tumor controls. They postulated that the reason for the greater frequency of persons homozygous for the high AHH inducibility allele in the lung cancer group was that this group was more susceptible to lung cancer due to their increased ability to convert polycyclic aromatic hydrocarbons into carcinogenic metabolites. The incidence of lung cancer,



however, does not show a markedly familial occurrence pattern; therefore, a single genetic locus can not be the major factor determining susceptibility. Persons with increased ability to metabolize polycyclic aromatic hydrocarbons may well be a group at increased risk of developing lung cancer if they smoke; however, prospective studies of random populations controlled for smoking and environmental factors will be necessary before this genetic susceptibility can be confirmed.

**FIGURE 1.—Production of aryl hydrocarbon hydroxylase (AHH) in macrophages from one person in response to cigarette smoking**



NOTE.—Shaded bar indicates duration of smoking; the vertical lines indicate the range of duplicate determinations at each time period.

Source: Cantrell, E.T., et al. (2).

**TABLE 3. – *Aryl hydrocarbon hydroxylase (AHH) inducibility in patients with lung cancer, with other tumors, and in healthy controls***

GROUP	NUMBER IN GROUP	DISTRIBUTION OF GENOTYPES ( PERCENT) <sup>1</sup>			GENE FREQUENCIES OF A AND B ALLELES	
		AA	AB	BB	A	B
Healthy control	85	44.7	45.9	9.4	0.676	0.324
Tumor control	46	43.5	45.6	10.9	0.663	0.337
Lung cancer	50	4.0	66.0	30.0	0.370	0.630

<sup>1</sup> AA = low inducibility; AB = intermediate inducibility; BB = high inducibility

Source: Kellerman, G., et al. (9).

## SUMMARY OF RECENT CANCER FINDINGS

1. Filter cigarette smokers have a lower risk of developing lung cancer than nonfilter cigarette smokers, but that risk is still greater than the risk to nonsmokers and increases with increasing number of filtered cigarettes smoked.

2. Cigarette smoking and exposure to radioactivity by uranium mining have been related to cytologic changes in the respiratory tract epithelium including carcinoma *in situ*. Cigarette smoking has been more strongly related to these changes than mining exposure.

3. Crysotile asbestos has been shown to contain traces of the carcinogen benzo(a)pyrene, and the combination of the two has been shown to be a more potent carcinogen in rats than either alone.

4. Heavy smoking prior to a first primary oral or respiratory cancer has been shown to be related to the development of a second primary in the respiratory tract or oral cavity.

5. Results from one study have shown a greater proportion of lung cancer patients having high levels of aryl hydrocarbon hydroxylase activity than among either healthy persons or persons with other cancers. Persons with high levels of AHH may be a group which has a genetically determined increased risk of lung cancer if they smoke, but no excess risk if they do not smoke.

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## **CHAPTER 3**

### **Non-Neoplastic Bronchopulmonary Diseases**

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## INTRODUCTION

Chronic non-neoplastic lung diseases are major causes of permanent and temporary disability in the United States. Chronic obstructive pulmonary disease (COPD) is the largest subgroup of these diseases and in this report refers to chronic bronchitis and/or emphysema. Relationships between smoking and non-neoplastic lung diseases have been reviewed in previous reports on the health consequences of smoking (36, 37, 38, 39, 40, 41, 42, 43).

Cigarette smoking is the most important cause of COPD. Cigarette smokers have higher death rates from chronic bronchitis and emphysema, more frequently report symptoms of pulmonary disease, and have poorer performance on pulmonary function tests than do nonsmokers. These differences become even more marked as the number of cigarettes smoked increases. The relationship between cigarette smoking and COPD has been demonstrated in many different national and ethnic groups and is more striking in men than in women. Pipe and cigar smokers have higher morbidity and mortality rates from COPD than do nonsmokers but are at lower risk than cigarette smokers. Cessation of cigarette smoking often results in improved pulmonary function tests, decreased pulmonary symptoms, and reduced COPD mortality rates.

In addition to an increased risk of COPD, cigarette smokers are more frequently subject to and require longer convalescence from other respiratory infections than nonsmokers. Also, if they require surgery, they are more likely to develop postoperative respiratory complications.

The relative importance of air pollution in the development of COPD remains controversial, but it is clearly less significant under most circumstances than cigarette smoking. The combination of cigarette smoking and polluted air, however, may produce higher rates of COPD than either factor alone.

Several occupational exposure groups incur an increased risk of COPD, and cigarette smoking adds significantly to this risk. In particular, exposure to cotton fiber and coal dust appears to act in concert with cigarette smoking to promote the development of pulmonary disease.

Autopsy studies have demonstrated a dose-related effect of cigarette smoking on the severity of macroscopic emphysema. Increased goblet cell density, alveolar septal rupture, bronchial epithelial thickening, and mucous gland hypertrophy are more commonly found in the lungs of smokers than in those of nonsmokers.

Many pathophysiologic mechanisms by which smoking may cause COPD have been proposed. Decreased overall pulmonary clearance, reduced ciliary motion, and impaired alveolar macrophage functions have all been related to cigarette smoking and probably play a role in the development of COPD. The exact mechanisms whereby cigarette smoking contributes to the development of COPD, however, remain only partially understood.

### **SMOKING AND RESPIRATORY MORBIDITY**

An increased prevalence of respiratory symptoms in smokers from early teens to those past the age of 80 has been well established. Bewley, et al. (5), in a study in Derbyshire County, England, extended these findings to include younger children. In a questionnaire study of 7,115 schoolchildren ages 10 to 11½ years, he found that 6.9 percent of the boys and 2.6 percent of the girls smoked more than one cigarette per day. The boys who smoked reported more morning cough (21.5% to 6.1%), cough during the day or night (48.0% to 20%), and cough of 3-months duration (18.0% to 4.1%) than their nonsmoking schoolmates. The percentages for the girls were similar although based on smaller numbers of smokers. As in many studies of this type, it was impossible to control for air pollution, social class, or smoking habits of the parents; nevertheless, the results suggest that cigarette smoking even in this young age group produces respiratory symptoms.

Fridy, et al. (12), in a somewhat older population (average age 25 years), examined the effect of smoking on airway function during mild viral illness. They measured closing volumes for 22 subjects (9 cigarette smokers — average age 29.1, and 13 nonsmokers — average age 25.7) before onset and at weekly intervals from the beginning of a mild respiratory illness until all symptoms had subsided. The closing volumes for smokers prior to illness were higher than those for nonsmokers, but the difference was not statistically significant. In the tests done during the illness, the smokers had a statistically significant increase in the closing volumes (from 37.0 to 45.8 percent of their total lung capacity, while nonsmokers had no change, 32.7

and 31.7 percent). Smokers remained symptomatic more than twice as long as nonsmokers (35.7 and 16.5 days, respectively), and the mean duration of pulmonary function abnormalities in smokers was 29.7 days. Nonsmokers had no change in pulmonary function tests during illness.

### **SMOKING AND AIR POLLUTION**

The relationships among air pollution, smoking, and COPD remain controversial. Reasons for this controversy include difficulties in controlling such variables as socioeconomic class, degree of crowding, ethnic differences, and age distribution as well as determining the exact type and amount of individual pollution exposure. Measuring individual pollution exposure even within a small area is difficult since both amount and type can vary dramatically from street to street (e.g., proximity of a street to a heavily traveled expressway).

In an effort to control as many of these variables as possible, two basic approaches in study design have been tried. The first approach is to find areas where pollution levels have been well measured and then to select study populations that are as similar as possible in areas with different pollution levels. Thus, effects on a population in a low pollution area can be compared to those on a similar population in a high pollution area. The second approach is to select a population that is as uniform as possible, for example, twins, and then measure individual responses to different pollution exposures. Both approaches have drawbacks as will be evident from the following studies.

Using the first approach, the Community Health and Environmental Surveillance System of the Environmental Protection Agency (6, 11), has conducted surveys in areas with different types and levels of pollution in four different parts of the United States (Chicago, New York City, the Salt Lake Basin, and the Rocky Mountain area). Within each part of the country, the researchers identified communities of similar socioeconomic status but different pollution levels. They then administered a questionnaire through the school systems to determine the frequency of lower respiratory tract infection in the children and their families. They reported an increased incidence of lower respiratory tract illness in children in high pollution communities compared to children in low pollution communities. This difference was demonstrable only in children whose families had lived in the high pollution communities for more than 3 years. They also reported an increased prevalence of chronic bronchitis in parents

who lived in high pollution communities compared to parents from low pollution communities. They calculated the excess risk of chronic bronchitis produced by air pollution to be one-third of that produced by smoking but to be additive with smoking.

Several major problems in these surveys make it difficult to evaluate the results. The authors describe the areas as having different kinds of pollution. The Salt Lake Basin and Rocky Mountain areas were felt to be high in sulfur dioxide (SO<sub>2</sub>) and low in total suspended particles (TSP), while New York and Chicago were high in both these pollutants. As a result, in the Salt Lake Basin and Rocky Mountain areas, communities were separated into low and high pollution communities only on the basis of their SO<sub>2</sub> levels. Many communities classified as low pollution communities on the basis of their SO<sub>2</sub> levels had higher levels of total suspended particles than the communities classified as high pollution communities by SO<sub>2</sub> level (Table 1). In fact, the average total suspended particles level for the low pollution communities in the Salt Lake Basin was higher than that for the high pollution communities (Table 2) in the Salt Lake Basin. These differences exemplify the difficulties of using only one pollutant as a marker of total pollution exposure.

Additional problems with these studies were the differences in socioeconomic class measurements between low and high pollution communities in some of the regions. In the Rocky Mountain area, the percentage of fathers who completed high school varied from 91 percent in one of the low communities to 58 percent in one of the high pollution communities. There were also major differences between high and low pollution communities in the percentage of families with more than one person per room in the Salt Lake Basin (59.6% to 51.2%), Rocky Mountain area (87.0% to 68.0%), and New York (85.0% to 72.0%). Residential stability (percentage of families living in the community for more than 3 years) was different in the high and low pollution communities in New York (58.0% to 36.0%) and Chicago (56.0% to 46.0%). The percentage of parents who currently smoke also differed for high and low pollution communities in New York (53% to 45% for the fathers and 47% to 37% for the mothers). These differences raise questions as to whether the high and low pollution communities were really similar enough populations to justify the claim that differences in incidence of respiratory tract illness could be attributable to differences in air pollution.

**TABLE 1. — Levels of sulfur dioxide (SO<sub>2</sub>) and total suspended particulates (TSP)  
in four Utah communities, 1971, and in five Rocky Mountain  
communities, 1970**

Area	Community Pollution Classification	Pollution levels in $\mu\text{g}/\text{m}^3$	
		SO <sub>2</sub>	TSP
Utah (Salt Lake Basin)	Low	8	78
	Intermediate 1	15	81
	Intermediate 2	22	45
	High	62	66
Rocky Mountain Area	Low 1	10	50
	Low 2	26	68
	Low 3	46	110
	High 1	109	43
	High 2	186	102

Source: Chapman, R.S., et al. (6).

**TABLE 2. – Mean annual levels of sulfur dioxide (SO<sub>2</sub>) and total suspended particulates (TSP) in four areas**

Area	Pollution levels in µg/m <sup>3</sup>							
	SO <sub>2</sub>				TSP			
	During Study		Decade Preceding Study		During Study		Decade Preceding Study	
	Low	High	Low	High	Low	High	Low	High
Five Rocky Mountain Areas	10	275	10	263	45	110	50	101
Salt Lake Basin	9	65	< 20	144	78	66	82	62
New York	23	63	< 30	431	34	104	40	201
Chicago	57	106	109	250	111	151	121	165

NOTE. – Area includes highest- and lowest-polluted communities.

Source: French, J.G., et al. (11).

Increased prevalence of COPD has also been demonstrated in areas of high pollution in the Netherlands (44), Yokkaichi, Japan (25), and Cracow, Poland (30). Again, however, these studies were poorly controlled for socioeconomic status.

Several recently published studies have used the second major method of investigating the relationship between smoking, air pollution, and COPD, i.e., to select a uniform population and then to measure individual differences to pollution exposure. Comstock, et al. (8), in an attempt to control for occupational exposure and socioeconomic class, studied three separate, uniform populations of telephone workers and used as a measure of pollution the location of the place of work and residence. The populations studied were telephone installers and repairmen in Baltimore, New York City, Washington, D.C., and rural Westchester County in 1962 (survey 1) and in 1967 (survey 2); and telephone installers and repairmen in Tokyo in 1967 (survey 3). They were unable to find any relation between pulmonary symptoms and degree of urbanization of place of work or place of residence (either current or past). They were, however, able to establish a strong correlation between smoking habits and pulmonary symptoms. Given the crude estimation of pollution exposure used in this study (all workers in each city were treated as though they received the same exposure), a small difference in symptoms due to air pollution could have been missed, whereas the difference due to smoking could be detected both because it was larger and because it was possible to determine individual exposure more exactly.

Hrubec, et al. (15), in a study of twins from the U.S. Veterans Registry, were unable to show a difference in respiratory symptoms either between individuals with different exposure to air pollution or between members of twin pairs with different air pollution exposures. However, they too used a crude measure of air pollution exposure (by each zip code area), and so could have missed a small difference due to air pollution despite being able to relate respiratory symptoms to smoking, socioeconomic status, and alcohol intake.

Colley, et al. (7), in a study of 3,899 persons (20-year-olds born during the last week of March 1946 in the United Kingdom), were also unable to show a relation between COPD and air pollution. They used as their estimates of air pollution exposure the domestic coal consumption in the towns where the subjects lived. This method of estimating air pollution exposure is subject to the same limitation cited for the previous two studies – limited sensitivity to small risks due to air pollution.

In summary, if an increased risk of COPD due to air pollution exists, it is small compared to that due to cigarette smoking under conditions of air pollution to which the average person is exposed. The possibility remains that the two different kinds of exposure may interact to increase the total effect beyond that contributed by each exposure.

## SMOKING AND OCCUPATIONAL DISEASE

Friedman, et al. (13), in a study of 70,289 men and women who had had Kaiser-Permanente multiphasic health checkups, noted that smokers were more likely to report occupational exposure on a questionnaire (Table 3) than nonsmokers. The differences are small but statistically significant and need to be considered when investigating the relationship of smoking to occupational diseases. They were not able to determine whether smokers' responses reflect actual differences in exposure or an increased awareness of and sensitivity to occupational exposure.

Exposure to coal and granite dust and cotton fiber carries an increased risk of COPD. This risk is further increased by cigarette smoking. Other new data have been published which clarify the risk in certain occupational groups.

### *Mill Workers – Byssinosis*

Berry, et al. (4), in a study of 595 workers in the Lancashire cotton mills over a 3-year period, found that the decline in forced expiratory volume in one second ( $FEV_1$ ) was 19 ml/year greater in smokers than in nonsmokers (59 ml/year compared to 40 ml/year,  $P > .02$ ) but they could not demonstrate a dose-response relationship.

### *Firemen*

Sidor and Peters (32, 33), in a cross-sectional study of 1,768 Boston firemen, were unable to show a significant relationship between severity of fire exposure and impairment of pulmonary function tests or prevalence of COPD; there was a clear harmful effect of cigarette smoking on both. They postulate that they were unable to show an increased prevalence of COPD in this cross-sectional study because firemen who developed COPD were no longer capable of meeting the physical demands of the job and had retired, thus removing them from the study population. They were able, however, to show a higher incidence of COPD in men under the age of 35 years who had been on the force more than 6 months when compared to persons of the same age who had just been hired.



**TABLE 3. — Age-adjusted percentage of cigarette smokers and nonsmokers in each race-sex group responding positively to exposure to chemicals, fumes, sprays, and dusts**

Exposure	Time period <sup>1</sup>	Smoking status	Whites		Blacks		Yellows	
			% Men	% Women	% Men	% Women	% Men	% Women
Chemicals, cleaning fluids or solvents (or chemical sprays) <sup>2</sup>	Before 1 year ago	Smokers	24.0	6.4	26.0	11.8	16.7	4.1
		Nonsmokers	18.9	5.1	19.2	6.7	12.9	5.1
	In the past year	Smokers	12.1	3.0	14.2	5.1	13.1	3.5
		Nonsmokers	9.7	2.6	11.6	4.5	9.4	3.8
Insect or plant sprays	Before 1 year ago	Smokers	4.0	1.0	6.6	2.1	3.8	0.3
		Nonsmokers	3.5	0.9	5.1	1.9	2.5	1.0
	In the past year	Smokers	2.9	2.1	4.8	2.9	3.0	1.3
		Nonsmokers	2.9	1.8	4.8	3.0	3.6	1.8
Ammonia, chlorine, ozone or nitrous gases (nitrous oxides or other irritating gases) <sup>2</sup>	Before 1 year ago	Smokers	7.9	2.3	10.3	4.8	6.2	0.9
		Nonsmokers	6.2	1.9	7.0	3.2	4.5	1.7
	In the past year	Smokers	5.4	1.9	7.6	3.9	8.0	0.5
		Nonsmokers	3.7	1.5	5.8	3.1	3.5	1.7
Engine or exhaust fumes (more than 2 hours a day) <sup>2</sup>	Before 1 year ago	Smokers	11.8	1.0	17.6	1.9	4.0	0.0
		Nonsmokers	6.9	0.5	13.1	0.6	3.6	0.1
	In the past year	Smokers	8.7	0.7	17.6	1.0	4.3	0.5
		Nonsmokers	5.2	0.5	13.3	1.2	3.9	0.2

TABLE 3. — Age-adjusted percentage of cigarette smokers and nonsmokers in each race-sex group responding positively to exposure to chemical, fumes, sprays, and dusts — Continued

Exposure	Time period <sup>1</sup>	Smoking Status	Whites		Blacks		Yellows	
			% Men	% Women	% Men	% Women	% Men	% Women
Plastic or resin fumes	Before 1 year ago	Smokers	5.1	1.1	3.3	1.2	3.1	0.1
		Nonsmokers	3.5	0.8	3.0	0.6	2.2	0.3
	In the past year	Smokers	3.3	0.8	3.9	0.9	3.0	0.1
		Nonsmokers	2.5	0.6	4.3	0.6	1.3	0.3
Lead fumes or metal fumes (lead sprays or paint sprays) <sup>2</sup>	Before 1 year ago	Smokers	8.2	0.9	9.1	1.5	4.1	0.1
		Nonsmokers	4.3	0.5	5.8	0.6	2.6	0.1
	In the past year	Smokers	5.5	0.7	7.7	1.3	3.3	0.5
		Nonsmokers	3.1	0.5	6.8	0.8	2.4	0.4
Asbestos, cement or grain (or flour) dusts <sup>2</sup>	Before 1 year ago	Smokers	7.1	0.6	11.5	1.2	2.7	0.0
		Nonsmokers	4.4	0.3	8.8	0.8	1.6	0.1
	In the past year	Smokers	2.8	0.4	7.5	1.0	2.7	0.1
		Nonsmokers	1.8	0.3	6.2	0.8	0.3	0.8
Silica, sandblasting, grinding or rock drilling dust (sand or coal) <sup>2</sup>	Before 1 year ago	Smokers	6.9	0.6	10.5	1.3	3.5	0.3
		Nonsmokers	4.0	0.5	6.8	0.7	2.9	0.0
	In the past year	Smokers	3.9	0.5	8.0	1.0	3.3	0.4
		Nonsmokers	2.3	0.4	6.6	0.9	3.5	0.4
Total number of subjects		Smokers	14,485	16,059	2,609	2,869	654	446
		Nonsmokers	8,282	18,526	1,116	3,218	712	1,313

<sup>1</sup>With a few slight variations, the questions were worded as follows:

Before 1 year ago: "Before 1 year ago have you ever worked in a place where you were often or daily around \_\_\_\_\_?"

In the past year: "In the past year have you worked in a place where you were often or daily around \_\_\_\_\_?"

<sup>2</sup>Material in parentheses appears in "past year" question but not in "before 1 year ago" question.

## SMOKING AND PULMONARY FUNCTION TESTS

It is recognized that smokers as a group have poorer pulmonary function tests than nonsmokers. The standard pulmonary function tests generally only become abnormal late in the pathologic process of COPD and usually only after irreversible changes in the lungs have occurred. As a result, tests are needed that will identify persons at risk of developing COPD before they have irreversible loss of lung function. Standard tests of pulmonary resistance are inadequate for this purpose because they measure predominately resistance in the large airways while the first changes of COPD occur in bronchioles that are 2 mm and smaller. Small airway resistance may be measured through evaluating frequency dependent compliance, but this is often cumbersome to perform. Closing volume and maximum expiratory flow rates at 25 and 50 percent of vital capacity have the advantage of being relatively easy to perform, yet are still able to measure changes in the small airways. Closing volume is the lung volume at which the alveoli in the dependent portions of the lung begin to close, and it is usually expressed as a percent of vital capacity. Elevated closing volume is considered evidence of small airway dysfunction. Maximum expiratory flow rates at 25 and 50 percent of vital capacity measure air flow at low lung volumes where the resistance of the small airways makes up a much larger proportion of the measured resistance.

Several recently published studies contain data on small airway dysfunction in smokers. Lim (20) studied 50 smoking and 50 nonsmoking high school students and found in smokers a statistically significant reduction in the forced expiratory volume in one second when the test was started at normal end expiration (i.e., low lung volumes). Stanescu, et al. (34) noted elevated closing volumes in 16 healthy asymptomatic smokers when compared to 16 nonsmokers, but were unable to show any difference in maximum expiratory flow rates at 25 and 50 percent vital capacity. Ruff, et al. (28) studied 50 subjects ages 18 to 82 and showed increasing closing volumes with age and smoking. Martin, et al. (21), in a study of 50 subjects ages 12 to 68, found that 25 percent of the smokers had abnormal closing volumes, and Oxhoj, et al. (26) noted elevated closing volumes for 50-year-old smokers compared to nonsmokers. Dirksen, et al. (10) reported higher closing volumes in smokers and noted no change with cessation of smoking. Hoepfner, et al. (14) also showed elevated closing volumes in healthy smokers ages 16 to 61, but found these to be closely related to decreases in the static transpulmonary pressure. They postulate that the elevated closing volumes may be related to decreased elastic recoil rather than changes in small airway resistance.

The data have established the fact that a greater percentage of smokers than nonsmokers have elevated closing volumes, but the number of smokers with elevated closing volumes who will develop COPD remains to be determined.

Stebbing (35), in a further analysis of Densen's data (9) on the changes in pulmonary function test values in male postal workers and transit workers in New York City, noted significantly less decline in FEV<sub>1</sub> among Black smokers when compared to White smokers. This difference persisted even when corrections were made for differences in amount smoked, age at which smoking began, inhalation patterns, and smaller initial lung volumes in Blacks. Black and White nonsmokers did not differ in the rate of decline in FEV<sub>1</sub>. By age 60 years, Blacks who smoked one pack per day had a .34 liter smaller cumulative decrease in FEV<sub>1</sub> than Whites who smoked the same amount.

### $\alpha_1$ -ANTITRYPSIN

It would be useful to identify the populations at excessive risk of developing COPD from smoking. They then might be made aware of the hazard before they develop symptomatic lung disease. Persons with  $\alpha_1$ -antitrypsin deficiency may be such a population.

$\alpha_1$ -antitrypsin deficiency is a rare homozygous recessive genetic defect which occurs in approximately one out of every 3,600 people and results in an increased susceptibility to and premature development of COPD. There is some evidence that smoking hastens the development of COPD in these people. The heterozygous state (producing intermediate levels of the  $\alpha_1$ -antitrypsin in serum) is far more common than the homozygous state and is found in approximately 10 percent of the population. It is uncertain whether the heterozygous deficiency state predisposes to COPD.

$\alpha_1$ -antitrypsin inheritance patterns suggest multiple codominant alleles at one gene locus, some of which (most notably the S and Z alleles) produce lower serum protease levels than the normal M-allele (Table 4). The pathophysiologic mechanism of the deficiency state is felt to be the inability to inhibit the proteases found in the granulocytes and pulmonary macrophages which go on to damage essential constituents of lung tissue. Several recent reviews of the enzyme and the clinical syndrome produced by its deficiency have been published (16, 17, 18).

**TABLE 4. — The  $\alpha_1$ -antitrypsin levels and frequency of protease inhibitor (Pi) phenotypes in healthy populations**

Protease inhibitor (Pi) type	Healthy populations	
	$\alpha_1$ -antitrypsin concentration (% normal)	Expected frequency of Pi types (per 1,000 people)
MM	100	898
(FM,FF,IM,MV,MX)	100	28
MW	80	— <sup>a</sup>
MP	80	1
MS	80	41
(FS,IS)	80	1
MZ	60	29
(FZ)	60	1
SS	55	1
SZ	40	1
ZZ	15	< 1

<sup>a</sup> Seen rarely in Spanish populations.

Source: Mittman, C., Lieberman, J. (22).

In most studies of patients with COPD, investigators have found an increased prevalence of the partially deficient heterozygote phenotypes when compared to healthy control populations. In the few studies not finding this relationship, only  $\alpha_1$ -antitrypsin levels were measured. Because  $\alpha_1$ -antitrypsin is an acute phase protein and increases with infection, it is difficult to separate out the partially deficient heterozygote phenotypes by measuring only  $\alpha_1$ -antitrypsin levels. It is necessary to identify the products of each allele electrophoretically in order to identify the deficient phenotypes.

Two recent studies using this technique showed an increased prevalence of deficient phenotypes in patients with COPD but not among control populations. Mittman, et al. (23) studied 240 patients with COPD admitted to LaVina Hospital in Altadena, California, and found that 19.1 percent had deficient phenotypes compared to only 7.1 percent of a control Scandinavian population. Keuppers and Donhardt (19) found prevalence rates for deficient phenotypes of 3.5 percent in healthy controls, 12.9 percent in persons retired from work because of COPD, and 15.7 percent in patients hospitalized for COPD.

Additional population studies have been done to determine the effect of the heterozygous state on the development of COPD. Webb, et al. (47) studied 500 persons visiting a multiphasic screening clinic in Monroe County, New York, and found that 11.6 percent had deficient phenotypes. He was unable to show differences in symptoms or in pulmonary function test values between persons with normal and deficient phenotypes. In a study of 451 randomly selected adults from the same county (31), pulmonary function studies were done on 40 deficient heterozygote phenotypes (20 MS and 20 MZ) and on normal phenotype (MM) controls matched for age, sex, and smoking habits. When total pulmonary resistance was measured by a forced oscillometric technique, the nonsmoking MZ subjects had significant impairment compared to their normal phenotype controls. All cigarette smokers, regardless of phenotype, had abnormal values.

Although the data are still inconclusive, it may well be that heterozygous deficient persons are a group at excessive risk of developing COPD especially if they smoke.

## AUTOPSY AND PATHOPHYSIOLOGIC STUDIES

### *Autopsy Studies*

Auerbach, et al. (3) have previously shown dose-related macroscopic emphysematous changes in the lungs of smokers. Now in an autopsy study (2) of 1,582 men and 388 women, they have examined microscopic lung parenchymal changes in relation to cigarette smoking. They were able to show that rupture of alveolar septa (emphysema) and fibrosis and thickening of the small arteries and arterioles are far greater in smokers than nonsmokers and increase with increasing amount smoked (Tables 5 and 6).

When these researchers examined former cigarette smokers, they found that those who had stopped more than 10 years prior to death had fewer pathologic changes than those who had stopped less than 10 years before death. But even in those who had stopped for more than 10 years, there was a greater degree of pathologic change in those who had been smoking more than one pack per day than in those who had been smoking less than one pack per day (Table 7).

Niewoehner, et al. (24), in an autopsy study of 39 men who died suddenly from various causes and who were below 40 years of age (20 nonsmokers and 19 smokers), observed a respiratory

**TABLE 5. — Means of the numerical values given lung sections at autopsy of male current smokers and nonsmokers, standardized for age**

	Subjects Who Never Smoked Regularly	Current Pipe or Cigar Smokers	Current Cigarette Smokers			
			< .5 Pk.	.5–1 Pk.	1–2 Pk.	> 2 Pk.
Number of Subjects	175	141	66	115	440	216
Emphysema	0.09	0.90	1.43	1.92	2.17	2.27
Fibrosis	0.40	1.88	2.78	3.73	4.06	4.28
Thickening of arterioles	0.10	1.11	1.35	1.66	1.82	1.89
Thickening of arteries	0.02	0.23	0.42	0.68	0.83	0.90

NOTE. — Numerical values were determined by rating each lung section on scales of 0–4 for emphysema and thickening of arterioles, 0–7 for fibrosis, and 0–3 for thickening of the arteries.

Source: Auerbach, O., et al. (2).

**TABLE 6. — Means of the numerical values given lung sections at autopsy of female current smokers and nonsmokers, standardized for age**

	Subjects Who Never Smoked Regularly	Current Cigarette Smokers	
		< 1 Pk.	≥ 1 Pk.
Number of Subjects	252	33	64
Emphysema	0.05	1.37	1.70
Fibrosis	0.37	2.89	3.46
Thickening of arterioles	0.06	1.26	1.57
Thickening of arteries	0.01	0.40	0.64

NOTE. — Numerical values were determined by rating each lung section on scales of 0–4 for emphysema and thickening of the arterioles, 0–7 for fibrosis, and 0–3 for thickening of the arteries.

Source: Auerbach, O., et al. (2).

TABLE 7. — Means of the numerical values given lung sections at autopsy of male former cigarette smokers, standardized for age

Formerly Smoked	Stopped $\geq$ 10 yr.		Stopped < 10 yr.	
	< 1 Pk.	Pk.	< 1 Pk.	Pk.
Number of Subjects	35	66	51	131
Emphysema	0.24	0.70	1.08	1.69
Fibrosis	1.14	1.74	2.44	3.30
Thickening of arterioles	0.57	0.93	1.25	1.59
Thickening of arteries	0.04	0.16	0.36	0.61

NOTE. — Numerical values for each finding were determined by rating each lung section on scales of 0–4 for emphysema and thickening of the arterioles, 0–7 for fibrosis, and 0–3 for thickening of the arteries.

Source: Auerbach, O., et al. (2).

bronchiolitis associated with clusters of pigmented alveolar macrophages in the lungs of smokers. They found these changes only rarely in the lungs of nonsmokers (Fig. 1). The smokers were young (average age 25.7 years), were a heavy smoking population (average 20.1 pack years), but did not differ significantly from the nonsmokers in age, social class, or pollution exposure. However, 12 of the 19 smokers had had productive cough or frequent cold compared to only 3 of the 20 nonsmokers. These authors postulated that bronchiolitis may be responsible for the abnormalities in the tests of small airway function of smokers.

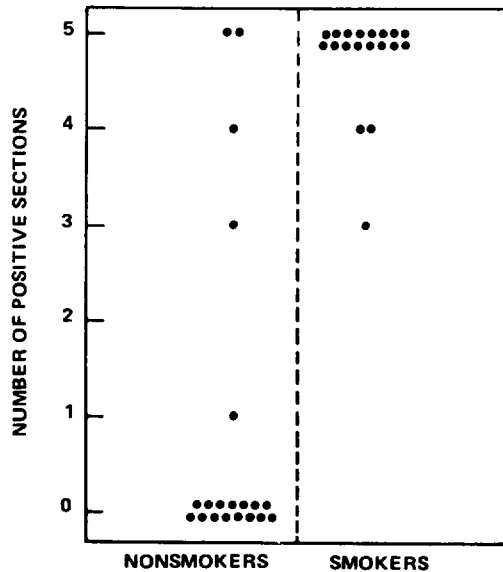
#### *Pathophysiologic Studies in Humans*

Yeager, et al. (48) showed decreased pinocytosis in human alveolar macrophages obtained from asymptomatic cigarette smoking volunteers when compared to those obtained from nonsmoking controls.

Warr and Martin (46) studied alveolar macrophages lavaged from four healthy smokers and four healthy nonsmokers. Only two members of each group were reactive to delayed hypersensitivity skin tests for *Candida albicans*. Macrophages from nonsmokers responded to Migration Inhibitory Factor (MIF) by a depression in migration of at least 30 percent, whereas macrophages from smokers did not respond to MIF. The cells from smokers were noted to migrate three times faster than those from nonsmokers. When *Candida* antigen was added to the medium, cells from the nonreactive subjects (both



**FIGURE 1.—Respiratory bronchiolitis in smokers and control group**



NOTE.—The position of each symbol represents the number of sections per case in which bronchiolitis was identified.

Source: Niewoehner, D.E., et al. (24).

smokers and nonsmokers) were not inhibited, the cells from the reactive nonsmokers were inhibited, but the cells from reactive smokers were not inhibited. Thus, macrophages from smokers did not respond normally to either MIF or antigenic challenge.

### *Pathophysiologic Studies in Animals*

Roszman and Rogers (27) noted that either the nicotine or the water soluble fraction of whole cigarettes smoked suppressed the immunoglobulin response of lymphoid cell cultures. When concentrations of over 200 micrograms per milliliter of nicotine of the water soluble fraction were added, they were able to completely suppress the immunoglobulin response and to observe this suppression even in cells exposed for 2 hours prior to the antigenic challenge.

Guinea pigs (29) exposed to the smoke of five cigarettes and then lavaged 2 hours later had fewer pulmonary macrophages and leukocytes in the lavage fluid than did controls not exposed to smoke. The decrease in the number of macrophages was highly correlated with acetaldehyde, tar, nicotine, hydrogen cyanide, and

acrolein concentrations in the cigarette smoke. The decrease in the number of leukocytes was more closely correlated with pH of the particulate phase and concentrations of acetaldehyde and tar.

Tracheal mucous velocity has been shown to be decreased in purebred beagle dogs (45) exposed to 100 cigarettes per week for 13.5 months. In donkeys (1) low level exposure to whole cigarette smoke accelerated tracheobronchial clearance, whereas at intermediate and high levels of exposure, clearance was decreased. At high exposure levels whole cigarette smoke had twice the effect of filtered smoke in decreasing clearance.

### **SUMMARY OF RECENT BRONCHOPULMONARY FINDINGS**

1. Cigarette smokers with mild viral respiratory illnesses have been shown to develop abnormal but reversible changes in certain pulmonary function tests while nonsmokers show no changes in these tests. Cigarette smokers have also been shown to have a significantly longer duration of respiratory symptoms following mild viral illness than nonsmokers.

2. Cigarette smoking is more closely related to COPD than is air pollution under the conditions of air pollution encountered by the average person. The possibility remains that the two kinds of exposure may interact to increase the total effect beyond that contributed by each exposure.

3. Cigarette smokers without respiratory symptoms have evidence of small airway dysfunction (elevated closing volumes) more frequently than do nonsmokers without respiratory symptoms.

4. Autopsy studies have shown a dose-response relationship between cigarette smoking and the microscopic changes of COPD. Data from one study indicate that bronchiolitis may be a far more common finding in cigarette smokers than in nonsmokers.

5. Pulmonary macrophages from cigarette smokers' lungs have a decreased ability to respond to in vitro antigenic stimuli as compared to macrophages from smokers.

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**CHAPTER 4.**  
**Involuntary Smoking**

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**Involuntary Smoking** \_\_\_\_\_

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## INTRODUCTION

The effects of smoking on the smoker have been extensively studied, but the effects of tobacco smoke on nonsmokers have received much less attention. The 1972 Health Consequences of Smoking (49) reviewed the effects of public exposure to the air pollution resulting from tobacco smoke. This exposure has been called "passive smoking" by many authors, but will be referred to in this report as "Involuntary Smoking." The term involuntary smoking will be used to mean the inhalation of tobacco combustion products from smoke-filled atmospheres by the nonsmoker. This type of exposure is, in a sense, "smoking" because it provides exposure to many of the same constituents of tobacco smoke that voluntary smokers experience. It is also "involuntary" because the exposure occurs as an unavoidable consequence of breathing in a smoke-filled environment.

The chemical constituents found in an atmosphere filled with tobacco smoke are derived from two sources — mainstream and sidestream smoke. Mainstream smoke emerges from the tobacco product after being drawn through the tobacco during puffing. Sidestream smoke rises from the burning cone of tobacco. Mainstream and sidestream smoke contribute different concentrations of many substances to the atmosphere for several reasons: Different amounts of tobacco are consumed in the production of mainstream and sidestream smoke; the temperature of combustion differs for tobacco during puffing or while smouldering; and certain substances are partially absorbed from the mainstream smoke by the smoker. The amount of a substance absorbed by the smoker depends on the characteristics of the substance and the depth of inhalation by the smoker. As discussed in the 1972 Report, when the smoker does not inhale the smoke into his lungs, the smoke he exhales contains less than half its original amount of water-soluble volatile compounds, four-fifths of the original nonwater-soluble compounds and particulate matter, and almost all of the carbon monoxide (15). When the smoker inhales the mainstream smoke, he exhales into the atmosphere less than one-seventh of the amount of volatile and particulate substances that were originally present in the smoke and also reduces the exhaled CO to less than half its original concentration (16). As a result, different concentrations of substances are found in exhaled mainstream smoke depending on the tobacco product, composition of the tobacco, and degree of inhalation by the smoker.

Several minor symptoms (conjunctival irritation, dry throat, etc.) are caused by levels of cigarette smoke encountered in everyday life, and serious allergic-like reactions to cigarette smoke may occur in some sensitive individuals. A major concern, however, about atmospheric contamination by cigarette smoke has been due to the production of significant levels of carbon monoxide. Cigarette smoking in poorly ventilated enclosed spaces may generate carbon monoxide levels above the acceptable 8-hour industrial exposure limits (50 ppm) – set by the American Conference of Government Industrial Hygienists (1). Exposure to this level of carbon monoxide even for short periods of time has been shown to reduce significantly the exercise tolerance of some persons with symptomatic cardiovascular disease. There is also some evidence that prolonged exposure to this level of carbon monoxide in combination with a high cholesterol diet can enhance experimental atherosclerosis in animals (Chapter 1, Cardiovascular Diseases).

In the present chapter, the effects of cigarette smoke on the environment and on the nonsmoker in that environment will be examined by reviewing data on (1) the constituents of cigarette smoke measured under various conditions, and (2) the physiologic effects of this “involuntary smoking” on individuals.

## CONSTITUENTS OF TOBACCO SMOKE

In a recent workshop on the effects of environmental tobacco smoke on the nonsmoker (41), Corn (14) presented a compilation adapted from Hoegg (32) of some of the substances in mainstream cigarette smoke and the ratio of sidestream to mainstream levels for some of these substances (Table 1). The actual numerical value of the sidestream to mainstream concentration ratio will vary with different types of tobacco tested, but Table 1 gives values generally consistent with those found by others (34, 42). Many of these substances including nicotine and carbon monoxide are found in much higher concentrations in sidestream smoke than in mainstream smoke, establishing that the smoke exposure received by both the smoker and nonsmoker due to breathing in a smoke-filled environment differs qualitatively as well as quantitatively from the smoke exposure received by the smoker who inhales through a lighted cigarette. A more comprehensive recent review of the constituents of mainstream and sidestream smoke has also been provided by Schmeltz, et al. (42) and Johnson, et al. (34).

TABLE 1. — Comparison of mainstream and sidestream cigarette smoke<sup>1,2</sup>

Compound		Mainstream (mg/cig)	Sidestream (mg/cig)	Ratio Sidestream/ Mainstream	Comment
A	General characteristics				
	Duration of smoke production	20 sec	550 sec	27	
	Tobacco burnt	347	411	1.2	
	Particulates, no. per cigarette	$1.05 \times 10^{12}$	$3.5 \times 10^{12}$	3.3	
B	Particulate phase				
	<sup>2</sup> Tar (chloroform extract)	20.8	44.1	2.1	
		10.2	34.5	3.4	Filter cigarette
	Nicotine	0.92	1.69	1.8	
		0.46	1.27	2.8	Filter cigarette
	Benzo(a)pyrene	$3.5 \times 10^{-5}$	$13.5 \times 10^{-5}$	3.7	
	Pyrene	$13 \times 10^{-5}$	$39 \times 10^{-5}$	3.0	
	Total phenols	0.228	0.603	2.6	
	Cadmium	$12.5 \times 10^{-5}$	$45 \times 10^{-5}$	3.6	
C	Gases and vapors				
	Water	7.5	298	39.7	3.5 mg of Mainstream and 5.5 mg of Sidestream in particulate phase, rest in vapor phase
	Ammonia	0.16	7.4	46	
	Carbon monoxide	31.4	148	4.7	
	Carbon dioxide	63.5	79.5	1.3	
	Oxides of Nitrogen	0.014	0.051	3.6	

<sup>1</sup> Adapted from Hoegg, U.R. (31, 32).

<sup>2</sup> For 35 ml puff volume, 2 sec puff duration, one puff per minute and 23 or 30 mm butt length and 10 percent tobacco moisture.  
Source: Corn, M. (14).

A number of other researchers have attempted to measure the levels of some of the substances in cigarette smoke encountered in everyday situations (Table 2). They have also tried to determine the factors controlling the atmospheric concentrations of these substances as well as the amount absorbed by nonsmokers under these conditions. Carbon monoxide, nicotine, benzo(a)pyrene, acrolein, and acetaldehyde have been of particular concern.

### *Carbon Monoxide*

Levels of carbon monoxide (CO), a major product of tobacco combustion, have been studied in a variety of situations, and concentrations ranging from 2 to 110 ppm have been measured (Table 2). The major determinants of the CO levels in these situations are size of the space in which the smoking occurs (dilution of CO), the number and type of tobacco products smoked (CO production), and the amount and effectiveness of ventilation (CO removal).

The type of tobacco product smoked is important as a determinant of CO exposure because it has been found that mainstream smoke from regular and small cigars contains more CO pre puff and per gram of tobacco burned than filtered or unfiltered cigarettes (8). This greater production of CO by cigars was confirmed by Harke (23). He measured the CO produced by 42 cigarettes, 9 cigars, and 9 pipefuls of tobacco, each product evaluated separately but under the same room conditions. The cigars produced the highest CO level (60 ppm).

In addition to the effect of type of tobacco product on CO levels, data on the effects of room size, amount of tobacco burned, and ventilation are included in Table 2. Only under conditions of unusually heavy smoking and poor ventilation did CO levels exceed the maximum permissible, 8-hour industrial exposure limit of 50 ppm CO (1); however, even in cases where the ventilation was adequate, the measured CO levels did exceed the maximum acceptable ambient level of 9 ppm (18).

Harke (27) also showed that in small enclosed ventilated spaces (an automobile) the CO level is determined more by the number of cigarettes being smoked at one given time than by the cumulative number of cigarettes that have been smoked; also the CO level decreases rapidly once the smoking stops.

**TABLE 2. — Measurements of constituents released by the combustion of tobacco products in various situations**  
**[ Cig = cigarettes; — = unknown; TPM = total particulate matter ]**

Reference, Location, and Dimensions If Known	Ventilation	Amount of Tobacco Burned	Constituents
Harke, H.-P., et al. (27) Mid-size European car, engine off, in wind tunnel at 50 km/hr wind speed	None	9 cig	30 ppm CO
	Air jets open & blower off	6 cig	20 ppm CO
	Air jets open & blower on	6 cig	10 ppm CO
	None	9 cig	110 ppm CO
	None	6 cig	80 ppm CO
	Air jets open & blower on	6 cig	8-10 ppm CO
Harke, H.-P., Peters, H. (28) Car in traffic	None	4 cig	21.4 ppm CO
Srch, M. (45) Car, engine off— 2.09 m <sup>3</sup>	None	10 cig in 1 hr	90 ppm CO, Smokers 10% COHb Nonsmokers 5% COHb
Seiff, H.E. (44) Intercity buses	15 air changes per hr	23 cig (burning continuously)	33 ppm CO (at driver's seat)
		3 cig (burning continuously)	18 ppm CO (at driver's seat)

TABLE 2. — *Measurements of constituents released by the combustion of tobacco products in various situations — Continued*  
 [Cig = cigarettes; — = unknown; TPM = total particulate matter]

Reference, Location, and Dimensions If Known	Ventilation	Amount of Tobacco Burned	Constituents
U.S. Dept. Transportation, et al. (48)			
Airplane flights:			
Overseas—100% filled	15-20 air changes per hr	—	2-5 ppm CO, <.120 mg/m <sup>3</sup> TPM
Domestic—66% filled	do.	—	<2 ppm CO, <.120 mg/m <sup>3</sup> TPM
Cano, J.P., et al. (11)			
Submarines—66 m <sup>3</sup>	Yes	157 cig per day 94-103 cig per day	<40 ppm CO, 32 µg/m <sup>3</sup> Nicotine <40 ppm CO, 15-35 µg/m <sup>3</sup> Nicotine
Godin, G., et al. (21)			
Ferry boat compartments:			
Smoking	—	—	18.4 ± 8.7 ppm CO
Nonsmoking	—	—	3.0 ± 2.4 ppm CO
Theater:			
Foyer	—	—	3.4 ± 0.8 ppm CO
Auditorium	—	—	1.4 ± 0.8 ppm CO
Bridge, D.P., Corn, M. (7)			
Party rooms:			
145 m <sup>3</sup>	7 air changes per hr	50 cig & 17 cigars in 1.5 hr	7 ppm CO
101 m <sup>3</sup>	10.6 air changes per hr	63 cig & 10 cigars in 1.5 hr	9 ppm CO

TABLE 2. -- *Measurements of constituents released by the combustion of tobacco products in various situations -- Continued*  
 [Cig = cigarettes; -- = unknown; TPM = total particulate matter]

Reference, Location, and Dimensions If Known	Ventilation	Amount of Tobacco Burned	Constituents
Harke, H.-P., et al. (25) Room--38.2 m <sup>3</sup>	None	30 cig per 13 min (by machine)	64 ppm CO, 510 µg/m <sup>3</sup> Nicotine .46 mg/m <sup>3</sup> Acrolein 6.5 mg/m <sup>3</sup> Acetaldehyde
		5 cig per 13 min (by machine)	11.5 ppm CO, 60 µg/m <sup>3</sup> Nicotine, .07 mg/m <sup>3</sup> Acrolein, 1.3 mg/m <sup>3</sup> Acetaldehyde
Harke, H.-P. (24) Office Bldg Office Bldg Room--78.3 m <sup>3</sup>	Air conditioned	--	<5 ppm CO
	Not air conditioned	--	<5 ppm CO
	--	3 smokers	15.6 ppm CO
Harke, H.-P., (23) Room--57 m <sup>3</sup>	None	42 cig (by machine)	50 ppm CO, 530 µg/m <sup>3</sup> Nicotine
	7.2 air changes per hr	42 cig do.	10 ppm CO, 120 µg/m <sup>3</sup> Nicotine
	8.4 air changes per hr	42 cig do.	<10 ppm CO, <100 µg/m <sup>3</sup> Nicotine
	None	9 cigars do.	60 ppm CO, 1040 µg/m <sup>3</sup> Nicotine
	7.2 air changes per hr	9 cigars do.	20 ppm CO, 420 µg/m <sup>3</sup> Nicotine
	None	9 pipes do.	10 ppm CO, 520 µg/m <sup>3</sup> Nicotine
	7.2 air changes per hr	9 pipes do.	<10 ppm CO, <100 µg/m <sup>3</sup> Nicotine



TABLE 2. — *Measurements of constituents released by the combustion of tobacco products in various situations — Continued*  
 [Cig = cigarettes; — = unknown; TPM = total particulate matter]

Reference, Location, and Dimensions If Known	Ventilation	Amount of Tobacco Burned	Constituents
Harke, H.-P. (23) Room—170 m <sup>3</sup>	None	105 cig	30 ppm CO, Smokers 7.5% COHb Nonsmokers 2.1% COHb
	1.2 air changes per hr	107 cig	5 ppm CO, Smokers 5.8% COHb Nonsmokers 1.3% COHb
	2.3 air changes per hr	101 cig	75 ppm CO, Smokers 5.0% COHb Nonsmokers 1.6% COHb
Anderson, G., Dalhamn, T. (3)	6.4 air changes per hr	46 cig & 3 pipefuls	4.5 ppm CO, 377 µg/m <sup>3</sup> Nicotine, 3.0 mg/m <sup>3</sup> TPM
Russell, M.A.H., et al. (40)	None	80 cig & 2 cigars per hr	38 ppm CO, Smokers 9.6% COHb Nonsmokers 2.6% COHb
Harmsen, H., Effenberger, E. (30)	None	62 cig in 2 hrs	80 ppm CO, 5200 µg/m <sup>3</sup> Nicotine
Hoegg, U.R. (31, 32)	None	4 cig	12.2 ppm CO, 2.28 mg/m <sup>3</sup> TPM
Ssealed test chamber—25 m <sup>3</sup>		8 cig	25.6 ppm CO, 5.39 mg/m <sup>3</sup> TPM
		16 cig	47.0 ppm CO, 11.41 mg/m <sup>3</sup> TPM
		24 cig	69.8 ppm CO, 16.65 mg/m <sup>3</sup> TPM

One must be careful when using the levels recorded in Table 2 as measures of individual exposure because the CO levels were usually measured at points several feet from the nearest smoker and probably would have been higher if measured at points corresponding to the position of a person sitting next to someone actively smoking (17, 35). In addition, it is the CO absorbed by the body that causes the harmful effects and not that which is measured in the atmosphere. This absorption can vary from individual to individual, depending on factors such as duration of exposure, volume of air breathed per minute, and cardio-respiratory function.

Several investigators have tried to determine the amount of carbon monoxide absorbed in involuntary smoking situations by measuring changes in carboxyhemoglobin levels in nonsmokers exposed to cigarette smoke-filled environments. Anderson and Dalhamn (3) were unable to find any change in the COHb levels of nonsmokers in a well ventilated room where the CO level was 4.5 ppm. When Harke (23) studied nonsmokers under similar conditions (good ventilation and less than 5 ppm CO), he was able to show an increase in COHb level from 1.1 to 1.6 percent; without ventilation the CO levels rose to 30 ppm and the COHb level increased from .9 to 2.1 percent in 2 hours. Russell, et al. (40) also found that COHb levels increased from 1.6 to 2.6 percent in nonsmokers exposed to a smoke-filled room where the CO level was measured at 38 ppm; however, he cautioned that nearly all persons in the room felt that the conditions were worse than those experienced in most social situations.

Stewart, et al. (46) measured COHb levels in a group of nonsmoking blood donors from several cities and found that 45 percent exceeded the Clean Air Act's Quality Standard of 1.5 percent with the 90 percent range as high as 3.7 percent for individual cities (Table 3). These levels represent the total CO exposure from all sources, involuntary smoking, and other sources of pollution as well as establishing the levels which would be added to any new involuntary smoking exposure.

Increases in the COHb levels of this magnitude are probably functionally insignificant in the healthy adult, but in persons with angina pectoris, any reduction of oxygen-carrying capacity is of great importance. In this disease, the volume of blood able to be pumped through the diseased coronary artery is already unable to meet the demands of the heart muscle under exercise stress. Aronow, et al. (4) examined the effect of exposure to carbon monoxide on persons with angina pectoris. They exercised persons with angina

**TABLE 3. — Median percent carboxyhemoglobin (COHb) saturation and 90 percent range for nonsmokers by location**

Location	Nonsmokers		No. of Nonsmokers	Percent of Nonsmokers With COHb > 1.5%
	Median	Range		
Anchorage	1.5	0.6 – 3.2	152	56
Chicago	1.7	1.0 – 3.2	401	74
Denver	2.0	0.9 – 3.7	744	76
Detroit	1.6	0.7 – 2.7	1,172	42
Honolulu	1.4	0.7 – 2.5	503	39
Houston	1.2	0.6 – 3.5	240	30
Los Angeles	1.8	1.0 – 3.0	2,886	76
Miami	1.2	0.4 – 3.0	398	33
Milwaukee	1.2	0.5 – 2.5	2,720	26
New Orleans	1.6	1.0 – 3.0	159	59
New York	1.2	0.6 – 2.5	2,291	35
Phoenix	1.2	0.5 – 2.5	147	24
St. Louis	1.4	0.9 – 2.1	671	35
Salt Lake City	1.2	0.6 – 2.5	544	27
San Francisco	1.5	0.8 – 2.7	660	61
Seattle	1.5	0.8 – 2.7	535	55
Vermont, New Hampshire	1.2	0.8 – 2.1	959	18
Washington, D.C.	1.2	0.6 – 2.5	850	35

Source: Stewart, R.D., et al. (46).

pectoris before and after exposure to carbon monoxide. The average amount of exercise that was able to be performed before a person developed chest pain was significantly shortened from 226.7 seconds before exposure to 187.6 seconds after CO exposure. This change occurred after a 2-hour exposure to 50 ppm CO and with an increase in COHb level from 1.03 percent to 2.68 percent; these COHb levels are within the range produced by involuntary smoking.

These data indicate that exposure to CO at levels found in some involuntary smoking situations may well have a significant impact on the functional capacity of persons with angina pectoris. Carbon monoxide has also been shown to decrease cardiac contractility in persons with coronary heart disease at COHb levels similar to those produced due to involuntary smoking situations (5). It is reasonable to assume that any significant CO exposure to the diseased heart reduces its functional reserve.

### *Nicotine*

Nicotine in the atmosphere differs from CO in that it tends to settle out of the air with or without ventilation (thereby decreasing its atmospheric concentration), whereas the CO level will remain constant until the CO is removed. The concentrations of both substances are decreased substantially by ventilation. As can be seen from data in Table 2, under conditions of adequate ventilation neither exceeds the maximum threshold limit values for industrial exposure (nicotine, 500  $\mu\text{g}/\text{m}^3$ ; CO, 50 ppm, 1); whereas in conditions without ventilation, smoking produces very high concentrations of both (nicotine, up to 1,040  $\mu\text{g}/\text{m}^3$ ; CO, 110 ppm).

Nicotine in the environment is of concern because nicotine absorbed by cigarette smokers is felt to be one factor contributing to the development of atherosclerotic cardiovascular disease. Several researchers have attempted to measure the amount of nicotine absorbed by nonsmokers in involuntary smoking situations. Cano, et al. (11) studied urinary excretion of nicotine by persons on a submarine. Despite very low levels measured in the air (15 to 32  $\mu\text{g}/\text{m}^3$ ), nonsmokers did show a small rise in nicotine excretion; however, the amount excreted was still less than 1 percent of the amount excreted by smokers. Harke (23) measured nicotine and its metabolite cotinine in the urine of smokers and nonsmokers exposed to a smoke-filled environment and reported that nonsmokers excreted less than 1 percent of the amount of nicotine and cotinine excreted by smokers. He feels that at this low level of absorption nicotine is unlikely to be a hazard to the nonsmoker.

### *Other Substances*

In two studies environmental levels of the experimental carcinogen benzo(a)pyrene were measured. Galuskinova (20) found levels of benzo(a)pyrene from 2.82 to 14.4 mg/m<sup>3</sup> in smoky restaurants, but it is not clear how much of this was due to cooking and how much was due to smoking. In a study of the concentration of benzo(a)pyrene in the atmosphere of airplanes (48), only a fraction of a microgram per cubic meter was detected. The effect of chronic exposure to very low levels of this carcinogen has not been established for humans.

Acrolein and acetaldehyde have also been measured in smoke-filled rooms (25, Table 2) and may contribute to the eye irritation commonly experienced in these situations.

## **EFFECTS OF EXPOSURE TO CIGARETTE SMOKE**

### *Cardiovascular Effects of Involuntary Smoking*

The effects of cigarette smoking on the cardiovascular system of the smoker are well established, but very little is known about the cardiovascular response of the nonsmoker to cigarette smoke. Harke and Bleichert (26) studied 18 adults (11 smokers and 7 nonsmokers) in a room 170 m<sup>3</sup> large in which 150 cigarettes were smoked or allowed to burn in ashtrays for 30 minutes. They noted that the subjects who smoked during the experiment had a significant lowering of skin temperature and a rise in blood pressure. Nonsmokers who were exposed to the same smoke-contaminated environment showed no change in either of these parameters. Luquette, et al. (36) performed a similar experiment with 40 children exposed alternately to smoke-contaminated and clean atmospheres, but otherwise under identical experimental conditions. They found that exposure to the smoke caused increases in heart rate (5 beats per minute) and in systolic (4 mm Hg) and diastolic (5 mm Hg) blood pressure. The differences in results between these studies may be due, in part, to the age of the subjects – i.e., children may be more sensitive to the cardiovascular effects of involuntary smoking than adults, or the increase in heart rate and blood pressure may be due to a difference between children and adults in the psychologic response to being in a smoke-filled atmosphere.

### *Effects of Carbon Monoxide on Psychomotor Tests*

Carbon monoxide from tobacco smoke, automobile exhaust, and industrial pollution is an important component of air pollution. There has been some concern over the effect of relatively low levels of carbon monoxide on psychomotor functions (the ability to perceive and react to stimuli), especially those functions related to driving an automobile (Table 4).

Carbon monoxide levels occasionally reached in some involuntary smoking situations result in measurable cognitive and motor effects, but these effects generally are measurable only at the threshold of stimuli perception. One study (Wright, et al., (50)) found that the safe driving habits measured on a driving simulator did not improve as much with practice in a group exposed to CO as did the habits of a control group. Another study (37) with a different experimental design but at the same levels of CO did not find any effect on complex psychomotor activity such as driving a car. Thus, the role of CO alone in motor vehicle accidents remains unclear. The effect on judgement and reactions of CO in combination with factors such as fatigue and alcohol, conditions known to influence judgement and reaction time, has not been determined.

### *Pathologic Effects of Exposure to Cigarette Smoke*

The effect of involuntary smoking on an individual is determined not only by the qualitative and quantitative aspects of the smoke-filled environment, but also largely by the characteristics of the individual. Reactions may vary with age as well as with the sensitivity of an individual to the components of tobacco smoke. The severity of possible effects range from minor eye and throat irritations experienced by most people in smoke-filled rooms, to the anginal attacks of some persons with cardiovascular disease.

The minor symptomatic irritation experienced by nonsmokers in a smoke-filled environment is influenced by the humidity of the air as well as the concentration of irritating substances found in the atmosphere. Johansson and Ronge (33) have shown that irritation due to cigarette smoke is maximal in warm, dry air and decreases with a small rise in relative humidity. A change from acceptable to unpleasant was reported at  $4.7 \text{ mg/m}^3$  of particulate matter for nonsmokers and eye irritation was noted at  $9 \text{ mg/m}^3$  for both smokers and nonsmokers. The authors concluded that a ventilation rate of  $12 \text{ m}^3/\text{hr}/\text{cig}$  was necessary to avoid eye irritation and  $50 \text{ m}^3/\text{hr}/\text{cig}$  was necessary to avoid unpleasant odors.

TABLE 4.— *Effects of carbon monoxide on psychomotor functions*

Reference	Test or Measurement	CO level (ppm)	COHb level (Percent)	Effect
McFarland, R.A. (37)	Ability of drivers to stay between two-lane markers while being permitted only brief glimpses of the road		6	None
			11	None
			17	None
Ray, A.M., Rockwell, T.H. (39)	Reaction time to car taillights		10	Prolonged
McFarland, R.A. (38)	Performance of two tasks at same time	700	17	None
	Dark adaptation and glare recovery	700	17	None
	Peripheral vision at 10° and 30°	700	17	None
	Peripheral vision at 20°	700	17	Decreased
	Depth perception	700	17	None
Stewart, R.D., et al. (47)	Time perception	500	20	None

TABLE 4. — *Effects of carbon monoxide on psychomotor functions — Continued*

Reference	Test or Measurement	CO level ppm	COHb level (Percent)	Effect
Fodor, G.G., Winneke, G. (19)	Attentiveness to auditory stimuli	50 x 5 hrs.	2-5	Decreased
	Flicker fusion	50 x 5 hrs.	2-5	No change
	Speed of motor performance	50 x 5 hrs.	2-5	No change
	Perception of complex visual patterns	50 x 5 hrs.	2-5	Improved
	Cognitive function	100	5	Decreased
Schulte, J.H. (43)	Reaction time		20	No change
Bender, W., et al. (6)	Threshold for temporal resolution of visual stimuli	100	7.25	Raised
	Manual dexterity	100	7.25	Decreased
	Learning meaningless syllables	100	7.25	Decreased
	Retention of 10 syllables for 1 hr	100	7.25	No change
Groll-Knapp, E., et al. (22)	Attentiveness to auditory stimuli	50		Deterioration at 50 ppm, worse at 100 ppm, worst at 150 ppm
		100		
		150		
Wright, G., et al. (50)	Reaction time		6.3	Prolonged
	Glare recovery		6.3	Prolonged
	Careful driving habits		6.3	Failure to improve with practice



Two government sponsored studies have attempted to evaluate the degree of minor irritation due to cigarette smoke experienced by bus and plane passengers. The U.S. Department of Transportation (44) studied the environment on two ventilated buses – one with simulated unrestricted smoking and another with simulated smoking limited to the rear 20 percent of the seats. In one bus, lighted cigarettes were placed at every other seat (23 cigarettes) to simulate a bus filled with smokers. In the other bus, cigarettes were placed only in the rear 20 percent of the bus (five cigarettes) to simulate a bus where smoking was limited to the rear 20 percent of the seats. When smoking was limited, the CO level at the driver's seat was only 18 ppm (ambient air 13 ppm) compared to the level of 33 ppm (ambient air 7 ppm) measured in the unrestricted smoking situation. Four of the six subjects seated in the bus reported eye irritation during the unrestricted smoking simulation. None of the six subjects reported any eye irritation in the restricted smoking situation (not even those seated in the rear 20 percent of the bus).

Several Federal agencies (48) cooperated to survey the symptoms experienced by travelers on both military and commercial aircraft. They distributed a questionnaire to passengers on 20 military and 8 commercial flights; 57 percent of the passengers on the military flights and 45 percent of the passengers on the commercial flights were smokers. The planes were well ventilated and CO levels were always below 5 ppm with low levels of other pollutants as well. In spite of the low level of measurable pollution, over 60 percent of the nonsmoking passengers and 15 to 22 percent of the smokers reported being annoyed by the other passengers' smoking. Seventy-three percent of the nonsmoking passengers on the commercial flights and 62 percent of the nonsmoking passengers on the military flights suggested that some remedial action be taken; 84 percent of those suggesting remedial action felt that segregating the smokers from nonsmokers would be a satisfactory solution. These feelings were even more prevalent among those nonsmokers who had a history of respiratory disease.

Children have been found to have a higher incidence of respiratory infections than adults and are thought to be more sensitive to the effects of air pollution due to their greater minute ventilation per body weight than adults. Several researchers have investigated the effects of parental smoking on the health of children. Cameron, et al. conducted two telephone surveys of Detroit families to determine the relationship between children's respiratory illness and parental smoking habits. In the first survey (9) they found a statistically significant relationship between the prevalence of

children's respiratory infection and parental smoking habits only when all children under 16 were considered (not when only those under 9 or under 5 were considered). In a larger survey of the same city (10) they found a relationship between parental smoking and prevalence of respiratory illness in the 10- to 16-year age group and in the birth to 5-year age group. Neither study controlled for smoking by the children which might be a factor in the 10- to 16-year age group or for socioeconomic status which has an effect on both smoking habits and illness. However, the data were consistent with a higher prevalence of respiratory disease in families where there are smokers than in nonsmoking families.

Colley (12) also found a relationship between parental smoking habits and the prevalence of respiratory illness in the children. He found an even stronger relationship between parental cough and phlegm production and respiratory infections in children. He postulates this latter relationship to result from the greater infectivity of these parents due to their cough and phlegm production. The relationship between parental cigarette smoking and respiratory infection in their children would then occur because cigarette smoking caused the parents to cough and produce phlegm and would not be indicative of a direct effect of cigarette smoke-filled air on the children.

Harlap and Davies (29) studied infant admissions to Hadassah Hospital in West Jerusalem and found a relationship between admissions for bronchitis and pneumonia in the first year of life and maternal smoking habits during pregnancy. Data on maternal smoking habits after the birth of the child were not obtained, but it can be assumed that most of the mothers who smoked during pregnancy continued to smoke during the first year of the infant's life. A relationship between infant admission and maternal smoking habits was demonstrable only between the sixth and ninth months of infant life and was more pronounced during the winter months (when the effect of cigarette smoke on the indoor environment would be greatest). Mothers who smoke during pregnancy are known to have infants with a lower average birth weight than the infants of nonsmoking mothers. The relationship between maternal smoking and their infants' admission to the hospital found in this study was greater for low birth weight infants, but was also found for normal birth weight infants (Table 5) (29). Harlap and Davies (29) demonstrated a dose-response relationship for maternal smoking and infant admission for bronchitis and pneumonia; however, they also found a relationship between maternal smoking and infant admissions for poisoning and injuries. This may indicate a bias in the study

TABLE 5. – Admission rates (per 100 infants) by diagnosis, birth weight, and maternal smoking

Diagnosis	Birth weight (g)						Total (including unknown)	
	<2,999		3,000 - 3,499		3,500+		S (986)	NS (9,686)
	S (297)	NS (2,326)	S (415)	NS (4,098)	S (264)	NS (3,195)		
Bronchitis and pneumonia	19.2	12.3	9.6	8.2	12.1	9.0	13.1	9.5
All other	22.6	19.9	14.5	14.6	15.2	13.3	16.9	15.5
Total	41.8	32.2	24.1	22.8	27.3	22.3	30.0	24.9

NOTE. – S=Smokers; NS=Nonsmokers.

Source: Harlap, S., Davies, A.M. (29).

due to relationships which may exist between smoking and factors such as parental neglect or socioeconomic class. In addition, hospital admission rates may not be an accurate index of infant morbidity.

Colley, et al. (13) studied the incidence of pneumonia and bronchitis in 2,205 children over the first 5 years of life in relation to the smoking habits of both parents. They found that a relationship between parental smoking habits and respiratory infection in children occurred only during the first years of life (Table 6). They also showed a relationship between parental cough and phlegm production and infant infection (Table 6) which was found to be independent of the effect of parental smoking habits. The relationship between parental smoking and infant infection was greater when both parents smoked and increased with increasing number of cigarettes smoked per day. The relationship persisted after social class and birth weight had been controlled for.

Thus, respiratory infections during the first year of life are closely related to smoking habits independent of parental symptoms, social class, and birth weight. Because of the dose-response relationship between parental smoking and infant respiratory infection established by Colley, et al. (13), it is reasonable to suspect that cigarette smoke in the atmosphere of the home may be the cause of these infections; however, other factors such as parental neglect may also play a role.

The above studies examined the effects of involuntary smoking on relatively healthy people. A substantial proportion of the U.S. population suffers from chronic cardiovascular and pulmonary diseases, however, and they represent the segment of the population most seriously jeopardized by conditions found in involuntary smoking situations. In Chapter 1 of this report (Cardiovascular Diseases) evidence was presented which showed that levels of CO sometimes experienced in smoke-filled environments (50 ppm) are capable of significantly decreasing the exercise tolerance of persons with angina pectoris and intermittent claudication. In addition, these levels of CO have been shown to decrease cardiac contractility and to raise left ventricular end-diastolic pressure (an indication of heart failure) in persons with cardiovascular disease.

Persons with chronic bronchitis and emphysema have considerable excess mortality under conditions of severe air pollution. In smoke-filled environments levels of CO and several other pollutants may be as high or higher than occur during air pollution emergencies. The effects of short-term exposure of persons with chronic obstruc-

TABLE 6. — *Pneumonia and bronchitis in the first 5 years of life by parents' smoking habit and morning phlegm*

Year of Followup	Annual incidence of pneumonia and bronchitis per 100 children (Absolute numbers in parentheses)									
	Both nonsmokers		One smoker		Both smokers		Both ex-smokers or one ex-smoker or smoking habit changed		All	
	N	O/B	N	O/B	N	O/B	N	O/B	N	O/B
1	7.6 (343)	10.3 (29)	10.4 (424)	14.8 (128)	15.3 (339)	23.0 (139)	8.2 (546)	13.2 (129)	10.1 (1,652)	16.7 (425)
2	8.1 (322)	8.3 (36)	7.1 (365)	15.5 (129)	8.7 (286)	9.2 (152)	6.5 (599)	10.7 (159)	7.4 (1,572)	11.3 (476)
3	6.9 (305)	8.1 (37)	10.5 (353)	9.4 (107)	7.9 (242)	11.0 (154)	8.2 (661)	11.6 (173)	8.4 (1,561)	10.6 (471)
4	8.0 (287)	11.1 (36)	7.5 (306)	10.8 (102)	7.6 (236)	11.6 (121)	8.2 (695)	9.1 (187)	7.9 (1,524)	10.3 (446)
5	6.7 (285)	14.7 (34)	5.6 (267)	9.4 (107)	3.9 (208)	10.6 (132)	6.4 (737)	7.3 (219)	5.9 (1,497)	9.1 (492)

NOTE. — N=neither with winter morning phlegm. O/B=one or both with winter morning phlegm.

Source: Colley, J.R.T., et al. (13).

tive bronchopulmonary disease (COPD) to these conditions have not been evaluated. Persons with COPD are also possibly at increased risk to CO exposure because of their low alveolar  $P_{O_2}$ . Due to the reduced amount of oxygen available to compete with the CO for hemoglobin binding sites, these persons might experience a carboxy-hemoglobin to oxyhemoglobin ratio higher than those in healthy subjects under the same conditions of CO exposure. The retention of CO may also be prolonged due to both this increased binding of CO to hemoglobin under low alveolar  $P_{O_2}$  and decreased ventilatory capacity to excrete CO.

In summary, the effects of cigarette smoke on healthy nonsmokers consists mainly of minor eye and throat irritation. However, people with certain heart and lung diseases (angina pectoris, COPD, allergic asthma) may suffer exacerbations of their symptoms as a result of exposure to tobacco smoke-filled environments. These effects are dependent on the degree of individual exposure to cigarette smoke which is determined by proximity to the source of the tobacco smoke, the type and amount of tobacco product smoked, conditions of room size and ventilation as well as the amount of time the individual spends in the smoke-filled environment, and his physiologic condition at the time of exposure.

## SUMMARY

1. Tobacco smoke can be a significant source of atmospheric pollution in enclosed areas. Occasionally under conditions of heavy smoking and poor ventilation, the maximum limit for an 8-hour work exposure to carbon monoxide (50 ppm) may be exceeded. The upper limit for CO in ambient air (9 ppm) may be exceeded even in cases where ventilation is adequate. For an individual located close to a cigarette that is being smoked by someone else, the pollution exposure may be greater than would be expected from atmospheric measurements.

2. Carbon monoxide, at levels occasionally found in cigarette smoke-filled environments, has been shown to produce slight deterioration in some tests of psychomotor performance, especially attentiveness and cognitive function. It is unclear whether these levels impair complex psychomotor activities such as driving a car. The effects produced by CO may become important when added to factors such as fatigue and alcohol which are known to have an effect on the ability to operate a motor vehicle.

3. Unrestricted smoking on buses and planes is reported to be annoying to the majority of nonsmoking passengers, even under conditions of adequate ventilation.

4. Children of parents who smoke are more likely to have bronchitis and pneumonia during the first year of life, and this is probably at least partly due to their being exposed to cigarette smoke in the atmosphere.

5. Levels of carbon monoxide commonly found in cigarette smoke-filled environments have been shown to decrease the exercise tolerance of patients with angina pectoris.

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## CUMULATIVE INDEX 1964—1975

Since the original report on the health consequences of smoking in 1964 entitled *Smoking and Health, Report of the Advisory Committee to the Surgeon General of the Public Health Service*, eight additional reports on the topic have been prepared for the U.S. Congress. The nine reports are for the years 1964, 1967, 1968, 1969, 1971, 1972, 1973, 1974, and 1975.

To facilitate use of this accumulated scientific evidence on the health consequences of smoking, the following cumulative index of the nine reports was prepared. It should be noted that before this cumulative index, the 1964 and 1968 Reports had not been indexed; thus, this compilation provides the only indexes for these two reports. The concept headings in this index are essentially the same as those used in the individual report indexes. However, an effort was made to use only one term per concept and to select the most commonly used terminology in the scientific literature for the concept.

The user of this index is referred to information in the different reports by the report year followed by the page numbers in that report. The year of the report is set in boldface type to stand out from the page numbers. The following excerpt from the index exemplifies this:

year	<div style="text-align: center;"> <p>Abortion comparison of stillbirth and neonatal death with, in smoking and nonsmok- ing mothers</p> <p><b>71</b> : 390,405-406</p> <p>effect of maternal smoking 71:13; 72:5, 84, 85; 73:123,124</p> </div>	pages
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71:390,405-406 (This entry refers the user to the 1971 Report, pages 390, 405, and 406.)

71:13; 72:5,84,85; 73:123-124 (This entry refers the user to the 1971 Report, page 13; to the 1972 Report, pages 5, 84, and 85; and to the 1973 Report, pages 123 and 124.)

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