The Health Consequences of SMOKING 1974

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

Public Health Service

Center for Disease Control

THE HEALTH CONSEQUENCES OF SMOKING

JANUARY 1974

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

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

Dear Mr. Speaker:

Enclosed is the 1974 report on the health consequences of smoking submitted to you as required by Section 8(a) of the Public Health Cigarette Smoking Act of 1969. As you will see, it confirms the evidence in previous reports that cigarette smoking is a serious health hazard and broadens our understanding of the mechanisms by which smoking contributes to the development of various forms of cancer, cardiovascular disease, and respiratory disease.

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

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PREFACE

This report is the eighth in a series issued by the Public Health Service reviewing and assessing the scientific evidence linking cigarette smoking to disease and premature death. The current report is devoted to recent research that enlarges the evidence on which our knowledge is based and broadens our understanding of the mechanisms whereby smoking contributes to the development of various forms of cancer, cardiovascular disease, and respiratory disease.

It is now 10 years since the Advisory Committee of the Surgeon General issued its famous report of January 11, 1964, and 20 years since scientific evidence indicating that cigarette smoking is a major health problem came to widespread public attention. In the past 20 years substantial changes have taken place in the smoking habits of the American public. In the early 1950's cigarette smoking had reached its peak as a habit among men in their 20's and was rapidly increasing as a habit among each succeeding generation of women.

As a result of the continuing growth of scientific evidence on the hazards of cigarette smoking and the educational programs to disseminate this knowledge, millions of people have stopped smoking, and millions of others who would otherwise have taken up smoking have not done so. A further gain in reducing the hazards has been the substantial decline in the "tar" and nicotine content of cigarettes in the past 20 years. Despite population increase and increase in the rate of smoking by young women, there has been a very real reduction in exposure to cigarettes in some portions of our society.

The evidence is clear that people who have stopped smoking cigarettes have lower death rates from smoking-related diseases than those who continue to smoke. If these reductions continue we can look forward to the time when the rapid increase of diseases associated with smoking will halt and begin a decline that will result in fewer deaths during the most productive years of life.

Charles C. Edwards, M.D.
Assistant Secretary for Health

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PREPARATION OF THE REPORT AND ACKNOWLEDGMENTS

Previous Reports

"Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service," subsequently referred to as the "Surgeon General's Report," was published in 1964. The National Clearinghouse for Smoking and Health, established in 1965, has the responsibility for the continuous monitoring, compilation, and review of the world's medical literature which bears upon the health consequences of smoking. As called for by Public Law 89–92, three subsequent reviews of the medical literature on the health consequences of smoking were sent to the Congress:

1. "The Health Consequences of Smoking, A Public Health Service Review: 1967" (submitted July 1967).
2. "The Health Consequences of Smoking, 1968 Supplement to the 1967 PHS Review" (submitted July 1968).
3. "The Health Consequences of Smoking, 1969 Supplement to the 1967 PHS Review" (submitted July 1969).

Public Law 91–222 was signed into law on April 1, 1970, and called for an 18-month interval between the 1969 supplement and the next report. During this period, a comprehensive review of all of the medical literature available to the Clearinghouse relating to the health consequences of smoking was undertaken, with an emphasis upon the most recent additions to the literature. The product of this review was: "The Health Consequences of Smoking, A Report of the Surgeon General: 1971," submitted to the Congress in January of 1971.

Subsequently, reviews of the medical literature, which had come to the attention of the Clearinghouse since the publication of the 1971 report, were published as, "The Health Consequences of Smoking, A Report of the Surgeon General, 1972," and "The Health Consequences of Smoking, 1973," and were submitted to the Congress in January of the corresponding years.

Every report published since the original "Surgeon General's Report" has contained a review of the medical literature relevant to the association between smoking and cardiovascular disease, non-neoplastic bronchopulmonary disease, and cancer. Several of the reports included reviews of the relationship between smoking and peptic ulcer disease (1967, 1971, 1972, 1973) and cigarette smoking and pregnancy (1967, 1969, 1971, 1972, 1973). Other topics relating to the use of tobacco have received special emphasis in single reports:

1. Noncancerous Oral Disease (1969).
2. Tobacco Amblyopia (1971).
3. Allergy (1972).
4. Public Exposure to Air Pollution from Tobacco Smoke (1972).
5. Harmful Constituents of Cigarette Smoke (1972).
6. Pipe and Cigar Smoking (1973).
7. Exercise Performance (1973).

The 1974 Report

The present document, "The Health Consequences of Smoking: 1974," includes reviews of the relationships between smoking and cardiovascular disease, chronic non-neoplastic bronchopulmonary disease, and cancer, which are based upon medical literature which has become available to the Clearinghouse since the publication of the 1973 report. Each chapter is organized in a similar fashion:

1. *Introduction.* Each introduction comprises a series of statements of the separate lines of evidence which converge to support a causal relationship between tobacco use and the specific diseases under consideration in the chapter. Each separate statement reflects critical reviews of the data available from the pertinent medical and scientific literature as presented in previous publications of "The Health Consequences of Smoking."
2. *Discussion.* The body of each chapter contains critical reviews of two types of articles which have come to the attention of the Clearinghouse in the interval since the publication of "The Health Consequences of Smoking: 1973."
   a. Those articles which either extend our understanding of the relationships between tobacco use and the specific

disease under consideration, beyond the position reflected in the introduction, or provide additional confirmation of previously suggested, but less well-established, relationships.

b. The articles which present new data which do not demonstrate the definite relationships between tobacco use and specific diseases identified by the critical review of previously available data.

3. *Summary.* The summary of each chapter includes statements of the most significant new contributions to the understanding of the relationships between tobacco use and specific diseases.

4. *Bibliography.* Each bibliography is divided into two parts. The first contains references to the studies discussed in the text; the second primarily contains references to those studies which form the bulk of the articles reviewed by the Clearinghouse, which have provided data confirming well-established relationships. Although these studies are not discussed in the text of the chapter, accession numbers from the "Smoking and Health Bulletin", published by the Clearinghouse, have been provided. The Bulletin contains abstracts of all of the articles obtained by the Clearinghouse each year, and the accession numbers provided in the supplemental bibliography of each chapter will direct the interested reader to the appropriate abstract. The Bulletin can be obtained from the Clearinghouse upon request.

Identification of Articles

For each report, the continuous monitoring and compilation of the medical literature on the health consequences of smoking has been accomplished through several mechanisms:

1. An information science corporation is on contract to extract articles on smoking and health from the medical literature of the world. This organization provides a semimonthly accessions list with abstracts and copies of the various articles. Translations are called for as needed. Articles are indexed and classified according to subject and filed in accession number order.

2. The National Library of Medicine, through the MEDLINE system, sends the National Clearinghouse for Smoking and Health a monthly listing of articles in the smoking and health area. These are reviewed, and the articles not

identified by the information science corporation are ordered.

3. Staff members review current medical literature and identify pertinent articles. Inevitably each year, articles containing important new data come to the attention of the Clearinghouse after the drafts of chapters have been submitted. Such articles are incorporated into the following year's report.

Review of Chapter Drafts

All of the articles so compiled related to cardiovascular disease, bronchopulmonary disease, and cancer were reviewed, and the first drafts of the chapters prepared by the medical staff of the National Clearinghouse for Smoking and Health. The first drafts were then sent to reviewers for criticism and comment with regard to the format, the thoroughness of screening the available literature, the selection and review of articles, and conclusions. The final drafts were reviewed as a whole by the Director of the National Clearinghouse for Smoking and Health, the Director of the National Cancer Institute, the Director of the National Heart and Lung Institute, the Director of the National Institute of Environmental Health Sciences, and by additional experts both within and outside of the Public Health Service.

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CHAPTER 1

CARDIOVASCULAR DISEASES

CORONARY HEART DISEASE (CHD)

Introduction

One million deaths per year are attributable to diseases of the cardiovascular system in the United States. Arteriosclerotic cardiovascular disease (ASCVD) is the leading cause of death in this country, accounting for greater than 50 percent of annual deaths; coronary heart disease (CHD) alone is responsible for 600,000 deaths per year. Cigarette smoking, hypercholesterolemia, and hypertension have been identified as major risk factors for the development of CHD.

Epidemiologic, autopsy, and experimental evidence presented in past editions of this report (1964, 1967, 1968, 1969, 1971, 1972, 1973) support a causal relationship between cigarette smoking and cardiovascular morbidity and mortality, as summarized below:

1. Both retrospective and prospective epidemiologic studies have demonstrated a strong relationship between cigarette smoking and increased CHD morbidity and mortality, with approximately a twofold higher risk of dying from CHD for all male cigarette smokers compared to nonsmokers.

2. A dose-response relationship has been demonstrated between cigarette smoking and CHD morbidity and mortality in men.

3. Cigarette smoking acts both independently of and synergistically with the other two major risk factors to produce these effects on CHD morbidity and mortality.

4. The above relationships between cigarette smoking and CHD morbidity and mortality have been demonstrated in Black and Asian, as well as Caucasian, populations.

5. The relative importance of cigarette smoking in the development of CHD in young men (less than 50 years old) is greater than that for any other risk factor.

6. Most prospective and retrospective studies suggest that pipe and cigar smokers exhibit a slightly higher risk of development of CHD than nonsmokers (but a significantly lower risk than cigarette smokers), while some studies demonstrate no such relationship.

7. Prospective epidemiologic studies document that cessation of cigarette smoking results in reduced mortality from CHD.

8. Autopsy studies reveal greater frequency and severity of coronary and aortic atherosclerosis among cigarette smokers than nonsmokers; cigarette smokers have been reported to have greater myocardial arteriolar wall thickening at autopsy than nonsmokers.

9. Experimental evidence in humans suggests that cigarette smokers with preexistent angina have a greater impairment in cardiac work capacity than nonsmokers. The role of cigarette smoking in the etiology of angina is unclear.

10. Experimental studies on humans and animals have shown that the pathophysiologic changes commonly observed in patients with CHD may be aggravated by cigarette smoking; contributions from both nicotine and carbon monoxide have been demonstrated. In addition, some of the biochemical and anatomical abnormalities seen in CHD have been induced by cigarette smoke, carbon monoxide, and nicotine.

Most of the studies reviewed in the last year confirmed the knowledge of the relationship between cigarette smoking and CHD. A listing of these studies appears in a separate section of the Supplemental Bibliography. A number of studies extended the knowledge of the association between cigarette smoking and CHD, but several studies presented data which were either partially or wholly inconsistent with the known relationships; these two types of studies are reviewed below.

Epidemiologic and Autopsy Studies

I. Studies in Men Demonstrating a Relationship Between CHD and Smoking.

The Coronary Drug Project Research Group studied, by multivariate analysis, 2,035 survivors of myocardial infarction in a prospective investigation to determine the relationship of placebo-treated premature beats and other known risk factors to sudden coronary deaths and total mortality (*CV 12*). Nonsmokers with ventricular premature beats (VPB) had a significantly higher total mortality than nonsmokers without VPBs ($P < .05$), and smokers with VPBs had a higher incidence of sudden coronary

deaths than smokers without VPBs ($P < .01$). Among patients without VPBs there was a significantly higher mortality rate in smokers compared to nonsmokers ($P < .05$). Even in the presence of VPBs, smokers had significantly higher total mortality ($P < .05$) than nonsmokers. A higher incidence of acute coronary deaths in smokers with VPBs compared to nonsmokers with VPBs was also found, but the difference was not statistically significant ($P \sim .08$). Thus, in survivors of myocardial infarction, smoking was associated with a significantly increased mortality, and when complicated by the presence of ventricular premature beats, resulted in an incidence of sudden death greater than the sum of the mortality from sudden death attributed to either risk factor (cigarette smoking or VPB) alone (figure 1). In this study, "lethal interactions" of this nature were found only for smoking, digitalis therapy, cardiac enlargement, and heart failure. These results indicate that cigarette smoking is an

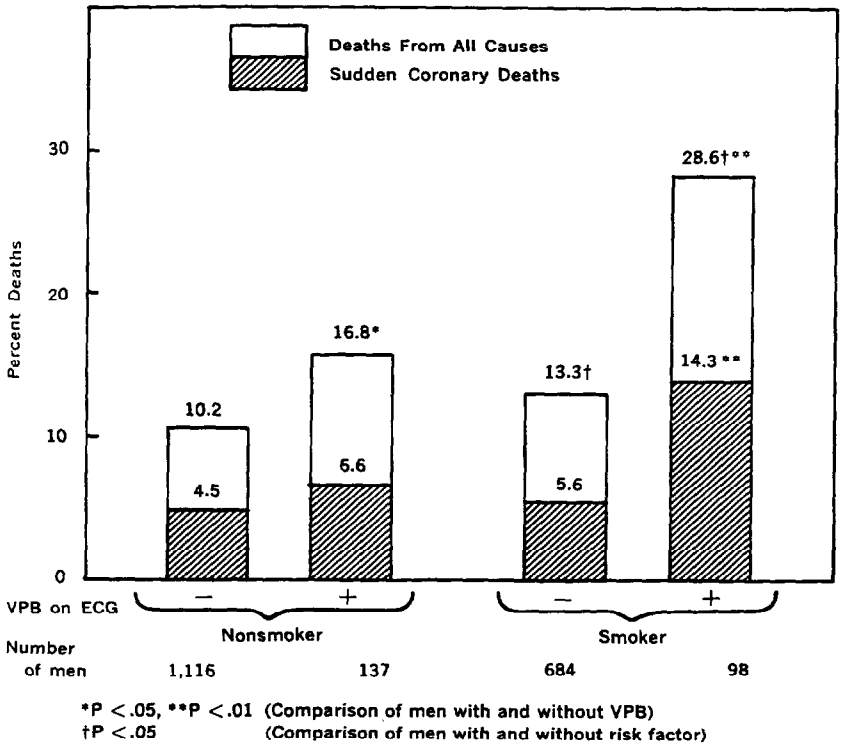

FIGURE 1.—Mortality for men with and without ventricular premature beats (VPB), according to presence or absence of smoking as a risk factor. Bars show percentages of men who died during 3-year period.

SOURCE: Coronary Drug Project Research Group (*CV12*).

important risk factor in the occurrence of sudden death as well as death from all causes among patients with known CHD.

In a recent article, Mennotti and Puddu (*CV 26*) reported on the 10-year follow-up data of the 1,717 men between the ages of 40 and 59 who were part of the Seven Countries Study. Whereas at five years, no relation could be found between the incidence of CHD and cigarette smoking, the 10-year follow-up data revealed a correlation between cigarette smoking and CHD, with a relative risk of 1.30–1.62 for smokers of greater than 10 cigarettes per day; the relative risk varied with the stringency of criteria for diagnosis of CHD and the degree of smoking. In these two populations, the incidence of CHD was far below that found in the United States, yet the current data suggest that cigarette smoking is a significant risk factor in the development of CHD in Italy.

With regard to the relative risks of the various risk factors, analysis of the 12-year follow-up data from The Peoples Gas Company Study (*CV 31*) revealed that in the cohort of 903 men free of CHD at the initial examination, the risk factor which was associated with the highest 12-year mortality from all causes was cigarette smoking, whether alone or in combination with the other risk factors (table 1). For all "CVR" (cardiovascular-renal), sudden, and CHD deaths there was a trend toward increased mortality in the smokers, but the total number of cases in each category was small.

Carlson and Bottiger (*CV 10*), in the Stockholm Prospective Study, examined 3,168 men and found that, over a 9-year follow-up period, the development of fatal and nonfatal myocardial infarction and other coronary deaths was related to cigarette smoking, elevated serum cholesterol, and elevated serum triglyceride concentrations. The incidence of new events of ischemic heart disease was significantly higher for all smokers ($P < .01$) and for smokers less than 60 years old ($P < .001$) compared to nonsmokers. Smokers aged 35 to 60 had significantly higher serum cholesterol and triglyceride levels, and higher blood pressure readings than nonsmokers.

In terms of CHD morbidity and mortality, cigarette smoking exerts its most potent effect on men under 60. Blacket, et al. (*CV 7*), in a retrospective study of 70 men in New South Wales with CHD, diagnosed between the ages of 28 and 40, demonstrated that 27 percent of this "coronary group" smoked more than 30 cigarettes per day as compared with 11 percent of the controls ($P < .001$). A total of 23 percent of the coronary group smoked more than 40 cigarettes per day ($P < .01$).

TABLE 1.—1958 serum cholesterol, diastolic blood pressure, cigarette smoking status, and 12-year mortality—cohort of 903 men, age 40 to 59 in 1958, free of evidence of organ system disease and ECG abnormalities and followed long-term without systematic intervention. Peoples Gas Company Study, 1958 to 1970.

Serum Cholesterol*	Diastolic Blood Pressure*	Cigarette Smoking*	No. of Men	12-Year Mortality									
				All causes		All CVR diseases		Sudden death		CHD		Stroke	
NH	NH	NH	208	15,†	69.9‡	2,	8.1	0,	0.0	2,	8.1	0,	0.0
H	NH	NH	106	11,	80.4	5,	40.2	1,	7.8	3,	21.3	1,	6.6
NH	H	NH	40	3,	72.6	1,	23.8	1,	23.8	1,	23.8	0,	0.0
NH	NH	H	289	38,	135.3	17,	61.3	6,	21.1	13,	46.5	4,	14.7
H	H	NH	34	4,	83.9	1,	20.8	0,	0.0	1,	20.8	0,	0.0
H	NH	H	154	26,	172.2	15,	98.2	7,	44.8	10,	63.5	4,	26.6
NH	H	H	40	8,	170.7	2,	42.1	1,	22.4	1,	22.4	1,	19.7
H	H	H	32	10,	319.3	4,	118.0	1,	26.3	3,	76.4	1,	41.6
1 only high			435	52,	118.0	23,	53.2	8,	18.7	17,	39.4	5,	11.2
Any 2 only high			228	38,	162.8	18,	78.5	8,	36.9	12,	53.5	5,	20.4
Any 2 or all 3 high			260	48,	182.2	22,	84.1	9,	35.3	15,	57.6	6,	22.2
All			903	115,	124.1	47,	51.8	17,	19.3	34,	37.7	11,	11.7

*NH, not high; H, high for serum cholesterol, ≥250 mg/dl at entry (1958); for diastolic blood pressure, ≥90 mm Hg at entry (1958); and for cigarette smoking, ≥10 cigarettes/day at entry (1958).

†Number of deaths.

‡Age-adjusted death rate/1000.

SOURCE: Stamler, J., et al. (*CV 81*)

The Boston Collaborative Drug Surveillance Program conducted a retrospective study on the prevalence of coffee drinking and cigarette smoking in 276 patients with a diagnosis of acute myocardial infarction (*CV 8*) and another study on 440 patients with acute MIs (*CV 21*) comparing these patients with hospitalized controls. On the basis of their data, they suggested that the association between coffee drinking and acute myocardial infarction was stronger than that between cigarette smoking and acute MI. There was observed an almost twofold risk of developing acute MI in noncoffee drinking patients who currently smoked more than 1 pack per day as compared with noncoffee drinking nonsmokers.

Hrubec (*CV 20*) reviewed data from the veteran twin panel of The National Research Council on patients with angina pectoris diagnosed by questionnaire, and found no significant correlation between coffee consumption and angina, except in the group smoking more than 1½ packs of cigarettes per day ($P < .03$). There was a significant relationship ($P < .05$) between cigarette smoking of any magnitude and the presence of angina.

II. Studies Failing to Demonstrate a Definite Relationship Between Smoking and CHD.

Cotton, et al. (*CV 13*), in a retrospective study, examined 91 men with a past history of myocardial infarction (4 months to 10 years). Case material was obtained from the files of two referring physicians in England, and controls were chosen from a regional transfusion service. These workers found no increased prevalence of MI among current smokers, but did report a significantly increased prevalence of MI in men with a past history of smoking ($P < .001$). The authors concluded that the lack of significant difference between the patients and controls in their "current" smoking habits ". . . probably reflects the fact that some of the patients gave up smoking or reduced the amount smoked after their coronary attacks."

Durakovic and Saric (*CV 15*), in a retrospective study of 998 Yugoslavian industrial employees, found no statistically significant correlation between cigarette consumption and the prevalence of angina pectoris.

Malhotra (*CV 25*) found no difference between current smoking habits in 44 patients with myocardial infarction and 88 hospitalized age- and sex-matched controls in an Indian population. A significant difference was found between cases and nonhospitalized healthy controls ($P = .02$).

Bruschke, et al. (*CV 9*) reported follow-up from 5 to 9 years after coronary arteriography of 590 consecutive patients with

significant coronary artery obstructive disease, and found a higher mortality rate in smokers compared to nonsmokers, but the difference was not statistically significant.

In New Guinea, Sinnett and Whyte (*CV 29*) reported a very low prevalence of CHD in a rural tribal area. The incidence of other known coronary risk factors was low, but tobacco was smoked by 73 percent and 20 percent of males and females, respectively. However, the authors emphasized that the tobacco leaf is dried and rolled into a bamboo pipe at least 6 inches long "and the smoke is not inhaled."

De Soldati, et al. (*CV 14*) conducted a retrospective study on 66 patients with recurrent myocardial infarction in Buenos Aires, and found a statistically significant correlation between cigarette smoking and recurrent myocardial infarction, but also reported that the nonsmokers had a significantly shorter interval between infarctions than the moderate or heavy smokers.

III. Studies in Women Relating CHD and Smoking.

Most of the studies on the relation between the various risk factors and CHD morbidity and mortality have been done with male populations. Data from large-scale studies have shown a relationship between CHD mortality and smoking in women. In a recent retrospective series of 182 women who died suddenly and unexpectedly, Spain, et al. (*CV 30*) reported a significant correlation between cigarette smoking and sudden death attributed to CHD. In this study, there were 29 CHD-related deaths. There was a significantly greater number of nonsmokers dying of non-CHD causes than of CHD ($P < .01$) (table 2). In addition, 62 percent of the women dying suddenly from CHD smoked greater than 1 pack per day, as opposed to 28 percent of the control group composed of women dying suddenly of other causes ($P < .01$). In the CHD group, there was an inverse relationship between the degree of cigarette consumption and mean age at death, i.e., heavy smokers died of CHD at an earlier age than nonsmokers. The statistical significance of this observation was not recorded. The authors reported that the mean age at the time of sudden death for the entire group of 182 women was 19 years less for heavy smokers compared to nonsmokers. The authors also reported that in their autopsy populations the male:female mortality ratio for sudden death due to CHD was 11:1 for nonsmokers and ~3.8:1 for all smokers.

TABLE 2.—*Cigarette smoking and sudden death from CHD in women*

	Population* Number/percent	CHD sudden death	
		Number/percent	Mean age/range
Smoking habits			
Nonsmoker	81/53	3/10	67/60–75
<20 cigarettes/day	29/19	8/28	55/52–61
≥20 cigarettes/day	43/28	18/62	48/32–58
Total	153/100	29/100	54/32–75

*All deaths exclusive of CHD.
SOURCE: Spain, D. M., et al. (*CV 30*).

Wink and Hager (*CV 35*), in a retrospective study of 10 premenopausal women with myocardial infarction, showed that there was a significantly higher incidence of cigarette smoking in this group of women than in postmenopausal women with acute myocardial infarction seen in the same clinic ($P < .001$).

CARBON MONOXIDE (CO)

Introduction

The importance of the effects of low levels of exposure to carbon monoxide on the pathophysiology of CHD is well recognized (1967, 1968, 1969, 1971, 1972, 1973).

It is known that the gas phase of cigarette smoke contains approximately 1 to 5 percent CO and that the concentration of CO increases as the cigarette burns down. Heavy cigarette smokers develop significantly higher COHb concentrations than nonsmokers, reaching levels of 4 to 15 percent. Arterial hypoxemia may develop following CO exposure, and myocardial metabolism may be significantly altered under the conditions of CO exposure, thus limiting myocardial work capacity. A significant decrease in exercise performance in patients with angina has been induced by smoking non-nicotine cigarettes, with increases of carboxyhemoglobin concentrations to approximately 8 percent. Some of the mechanisms responsible for these effects have been reviewed in previous editions of this report.

In experimental studies, CO increases coronary flow and heart rate in normal subjects, increases oxygen debt, and results in myocardial hypoxia. Carbon monoxide has also been implicated by some workers as an etiologic factor in the development of atherosclerotic lesions. Recent studies have contributed significantly to our understanding of the role of CO in the development and pathophysiology of CHD.

Epidemiologic Studies

Wald, et al. (*CV 34*) found, in cross-sectional analysis of 950 Danish smokers, a correlation between the development of atherosclerotic diseases and carboxyhemoglobin levels. They concluded that COHb levels were better indicators than smoking history of a person's risk of developing ASCVD, including CHD. The heavy smokers had a higher prevalence of ASCVD than the nil and light smokers combined ($P < .001$). Only 8 of the 58 subjects had a past history of myocardial infarction.

Experimental Studies in Man

Aronow, et al. (*CV 3*) studied the effect of carbon monoxide exposure on myocardial work capacity and angina. Ten men with known CHD and angina, aged 40 to 56, who were exposed to heavy morning freeway traffic in Los Angeles for 90 minutes, performed cardiopulmonary tests in the pre-exposure, immediate post-exposure, and 2-hour post-exposure states. Each man served as his own control by breathing purified compressed air on a similar 90-minute excursion in heavy morning traffic. After breathing the freeway air, all 10 men developed marked increases in expired-air carbon monoxide levels ($P < .001$), and arterial carboxyhemoglobin levels ($P < .001$), both immediately and at 2 hours post-exposure. No differences were found in these parameters when the patients breathed compressed air. The mean exercise performance of the 10 men was significantly impaired in the immediate post-exposure period ($P < .001$) and also at 2 hours post-exposure ($P < .05$). The mean exercise performance was significantly increased from the immediate post-exposure period to the 2-hour post-exposure period ($P < .05$), corresponding to significant decreases in mean expired CO and percent COHb at 2-hours post-exposure. Significant decreases in heart rate ($P < .001$), systolic blood pressure ($P < .01$), and the product of the systolic blood pressure times the heart rate ($P < .001$) developed in relation to the onset of angina in the immediate post-exposure period, and significant decreases were noted at the time of onset of angina at the 2-hour post-exposure periods for heart rate ($P < .001$) and the BP x HR product ($P < .001$). No significant differences in any of these values were found when the patients breathed compressed air. Three of the 10 patients developed ischemic ST segment depression during the ride of carbon monoxide exposure; none of the 10 patients developed such changes during exposure to compressed air. As the BP x HR product is one measure of cardiac work capacity, these results strongly suggest that "less work can be done before the onset of

exercise-induced angina in patients with elevated carboxyhemoglobin levels" (as manifested by diminution of both cardiac work measurements and actual exercise performances). Pollutants other than carbon monoxide may have contributed to the findings in this study.

Using a double-blind design, Aronow and Isbell (*CV 4*) studied the effects of the administration of purified CO and purified compressed air on 10 men with stable angina. All the subjects were nonsmokers. Administration of the compressed air for 2 hours resulted in a significant decrease of venous COHb ($P < .001$) from a mean of 1.07 percent to 0.77 percent and no significant changes in mean exercise time until onset of angina, systolic blood pressure (BP), heart rate (HR), or the BP x HR product. Administration of 50 p.p.m. CO for 2 hours resulted in a significant increase in venous COHb ($P < .001$) from a mean of 1.03 percent to 2.68 percent, and significant decreases in mean exercise time until onset of angina ($P < .001$) systolic blood pressure, heart rate, and the BP x HR product at the time of angina ($P < .001$). It is important to note that the levels of carboxyhemoglobin observed in the groups of patients from these two studies were below those frequently attained by cigarette smokers.

In a related study, Fortuin, et al. (*CV 1, 2, 16*) analyzed mid- and post-exercise ECG changes in "normal" subjects and patients with stable angina before and after exposure to purified CO. In the "normal" subjects, venous COHb concentrations of 5.7 to 7.1 percent were obtained, and exercise performance, as measured by time period of exercise before attaining a specified heart rate, was significantly impaired in both young ($P < .005$) and middle-aged subjects ($P < .01$). Seven of the 26 older "normal" subjects demonstrated some abnormality in their ECGs at some stage in the study, and all of these ECG changes (including ST segment abnormalities and arrhythmias) were exaggerated after CO exposure. In the 10 patients with stable angina, venous COHb levels were raised to 2.9 and 4.5 percent after exposure to 50 and 100 p.p.m. CO, respectively. The mean duration of exercise before the onset of anginal pain was significantly shortened following CO exposure at both dose levels ($P < .005$), ST segment depression was deeper in 5 of 10 patients, and, in general, had an earlier onset and longer duration after CO exposure. In addition, duration of pain was significantly lengthened with exposure levels of 100 p.p.m. ($P < .01$). These studies lend further support to the concept that CO exposure resulting in mild to moderate elevations in COHb concentrations may exacerbate exercise-

induced myocardial ischemia in persons with preexisting clinical or subclinical coronary heart disease.

NICOTINE

Nicotine has been found to increase heart rate, blood pressure, cardiac output, stroke volume, and velocity of myocardial contraction. The cardiovascular effects of nicotine has been summarized in The Health Consequences of Smoking (1971). Experimental evidence suggests that these effects are mediated through release of catecholamines from sympathetic ganglia and myocardial chromaffin tissue, and that sympathetic ganglionic blockers inhibit these effects. There may also be neurogenic components to the cardiovascular effects of nicotine, as well as effects on regional coronary perfusion.

Experimental Studies

Bizzi, et al. (*CV 6*) studied the effects of nicotine on adipose tissue in the rat. Rats were administered nicotine intraperitoneally and subcutaneously, and the responses of plasma free fatty acids (FFA) and in vitro lipolysis were observed. Intraperitoneal nicotine tartrate (NT) caused a transient rise in FFA, and subcutaneous NT in 1 percent carboxymethylcellulose also resulted in a rise in plasma FFA in a dose-response relationship. Administration of the vehicle alone as a control was not performed. Inhibitors of lipolysis (including beta blockers) inhibited this stimulatory effect of nicotine on plasma FFA. Of particular note was that in adrenalectomized rats, NT failed to elevate plasma FFA, but did so when corticosterone was administered before sacrifice.

In vitro, NT added to a medium containing adipose tissue did not result in enhanced release of FFA into the medium, thereby implying an indirect effect of NT through enhanced catecholamine secretion as seen in the in vivo situation. Neither acute nor chronic doses of NT resulted in elevated tissue triglyceride concentrations.

These results confirm previous evidence of nicotine's ability, both acutely and chronically, to elevate plasma FFA, this action being mediated through enhanced catecholamine secretion. The new findings concerning the role of adrenocorticoids are of uncertain significance. The precise role of elevated FFAs in atherogenesis remains to be elucidated.

PERIPHERAL VASCULAR DISEASE

A number of retrospective studies have implicated cigarette smoking as one of the major risk factors in the development and progression of peripheral atherosclerosis, arteriosclerosis obliterans (ASO) and thromboangiitis obliterans (TAO). The patency of peripheral bypass grafts may also be adversely affected by cigarette smoking.

The increased incidence of peripheral vascular disease associated with smoking may be in part due to elevated COHb levels. Experimental data suggest that cigarette smoking may chronically decrease peripheral flow capacity and acutely result in closure of precapillary sphincters, vasoconstriction, and decreased blood flow in human connective tissue in vivo.

Recent prospective and retrospective epidemiologic evidence, as well as experimental data add to our knowledge of the association between cigarette smoking and peripheral vascular disease.

Epidemiologic Studies

The 16-year follow-up data of the Framingham Study (*CV 18*) revealed strong relationships between cigarette smoking and the development of the three major manifestations of atherosclerosis: CHD, atherosclerotic brain infarction (ABI), and intermittent claudication (figure 2). The only exception to this was the absence of correlation between cigarette smoking and ABI in women, but for CHD deaths, MI, coronary insufficiency, and intermittent claudication, the correlations were as strong in women as in men. It appears that cigarette smoking is one of the major risk factors in the development of intermittent claudication (table 3) (*CV* 24). A higher total incidence over the 16 years of follow-up and a higher annual incidence of intermittent claudication occurred in smokers than in nonsmokers, the latter statistically significant for all age groups of both sexes. When the other risk factors were controlled for utilizing multivariate analysis, the effect of smoking became even more pronounced.

In a retrospective study of 100 patients with peripheral vascular disease evaluated by peripheral angiography and selective coronary angiography, Tomatis, et al. (*CV 32*) found that 98 percent of patients with aortoiliac disease, 91 percent of those with femoropopliteal disease, and 93 percent with abdominal aortic aneurysms had a history of smoking.

In a population of nondiabetic smokers with evidence of peripheral vascular disease, Linhart, in Astrup, et al. (*CV 5*), found

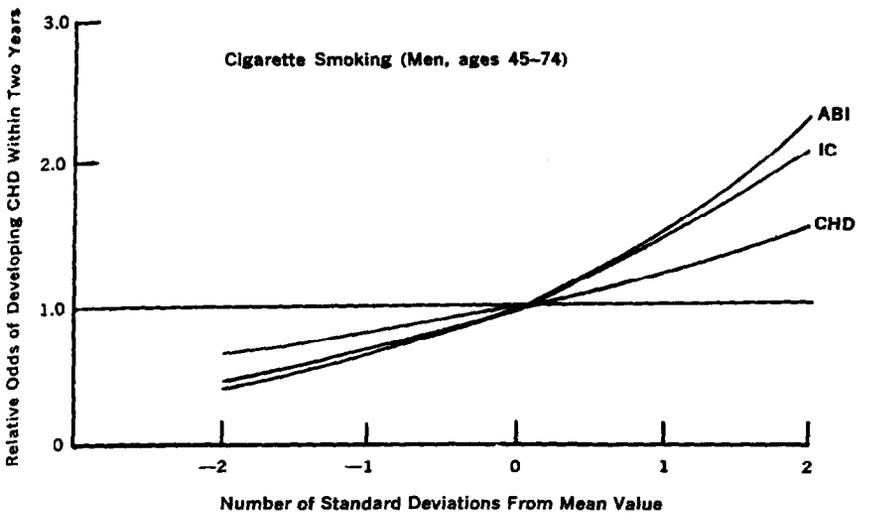

FIGURE 2.—Relative odds of developing atherothrombotic brain infarction (ABI), coronary heart disease (CHD), or intermittent claudication (IC) according to levels of cigarette smoking.

SOURCE: Gordon, T., Kannel, W. B. (*CV 18*).

TABLE 3.—*Standardized multivariate regression coefficients of intermittent claudication for various characteristics*

Characteristic	Regression coefficient			Mean (and standard error)
	Age 45-54	Age 55-64	Age 65-74	
Men				
Cigarettes/day	0.362	0.618	0.016	0.451 (0.115)
Glucose intolerance	0.323	0.410	−0.115	0.351 (0.075)
Serum cholesterol	0.303	0.314	−0.103	0.259 (0.092)
Systolic blood pressure	0.105	0.318	−0.412	0.178 (0.107)
Left ventricular hypertrophy (ECG)	0.118	0.016	0.231	0.080 (0.087)
Women				
Cigarettes/day	0.731	0.270	0.462	0.405 (0.126)
Glucose intolerance	----	0.442	0.232	0.390 (0.101)
Serum cholesterol	0.404	0.286	0.113	0.334 (0.096)
Systolic blood pressure	0.540	0.247	0.420	0.356 (0.136)
Left ventricular hypertrophy (ECG)	0.242	0.223	0.304	0.247 (0.097)

Note: Incidence of intermittent claudication:

	45-54	55-64	65-74
Men	20	45	15
Women	5	21	12

SOURCE: Kannel, W. B., Shurtleff, D. (*CV 24*).

a significant correlation between frequency of severe intermittent claudication and consumption of greater than 15 cigarettes per day ($P < .01$). There was no difference between these heavy smokers and the other smokers for development of gangrene, nor did development of claudication vary with number of years smoking or total number of lifetime cigarettes consumed. Of his 112 patients, 57 stopped smoking after initial diagnosis and treatment, and subsequent progress of their claudication was retarded with no fresh gangrene developing in any of these subjects. The 55 patients who continued smoking suffered from the same rate of complications as seen before treatment.

Experimental Studies

Goldman, et al. (*CV 17*) reported that the amount of heat loss from the hands of 10 normal subjects was found to be significantly less on exposure to cold after subjects smoked two cigarettes, when compared to the control state ($P < .05$). Smoking exerted no effect on heat loss from the feet of these subjects. These results corroborate previous reports of the vasoconstrictive effects of smoking on the peripheral vasculature. The differences in heat loss between upper and lower extremities were explained by differences in reactivity to vasomotor stimuli, differences in total blood flow, and greater vasoconstrictor tone in the lower extremity.

CEREBROVASCULAR DISEASE (CVD)

Retrospective studies have revealed a correlation between cigarette smoking and morbidity and mortality from CVD in men. No correlation has been found previously for women.

Acutely, cigarette smoking has been reported to increase cerebral flow and decrease cerebrovascular resistance. The exact role of cigarette smoking in the pathogenesis of CVD is unclear. Recent studies are summarized below:

Epidemiologic Studies

Data from a restrospective series of 598 nonpregnant women, ages 15 to 44, with a diagnosis of stroke (*CV 11*) revealed that 73 percent of the women with strokes were cigarette smokers as opposed to 43.4 percent of the nonhospitalized control group ($P < .001$) and 60 percent of the hospitalized control group ($P < .001$). The combined effect on thrombotic episodes in this study population of both smoking and oral contraceptives was greater

than that exerted by the use of oral contraceptives alone. It was concluded that cigarette smoking contributes significantly to the development of stroke in women, and enhances the effect of oral contraceptives on the development of thrombotic cerebrovascular events.

Analysis of the 16-year follow-up data of the Framingham study (*CV 23*) revealed an increased risk of ABI attributable to smoking in men, with a sixfold excess risk in male smokers aged 45 to 54. The numbers of cases are still too small to draw any firm conclusions from the data. No correlation between smoking and cerebrovascular events was found in women.

In a prospective study of 3,991 longshoremen followed for 18 years, Paffenbarger (*CV 28*) found no correlation between fatal stroke and cigarette consumption. Included in the study group were 59 cases (from a total of 132) of intracerebral hemorrhage.

CIGARETTE SMOKING AND ASSOCIATED CHD RISK FACTORS

There is conflicting evidence concerning the role of cigarette smoking in the chronic elevation of serum lipids. Results from studies of the acute effects of smoking on blood lipids, including FFA, cholesterol, and triglycerides, have also been contradictory.

A negative correlation between cigarette smoking and mean systolic and diastolic blood pressures has been shown in some studies and not others. This apparent correlation has been explained by the negative association between smoking and relative weight.

Recent contributions in this field are summarized below:

In a retrospective study of 42,804 military men in Belgium (*CV* 33), multiple regression analysis revealed that in all age groups smokers of greater than 20 cigarettes per day had a higher serum cholesterol than nonsmokers. This finding was of statistical significance in age groups 20 to 29 ($P < .01$), 30 to 39 ($P < .001$), and 40 to 49 ($P < .01$); i.e., the years of greatest risk of CHD for the combination of hypercholesterolemia and cigarette smoking (figure 3).

Mundy and Cutforth (*CV 27*) studied 85 patients with myocardial infarctions who had survived their infarctions for at least six months. They found no correlation between "lipid levels" and smoking. Only lipoprotein electrophoretic abnormalities were reported, although the authors stated that serum cholesterols and triglycerides were determined.

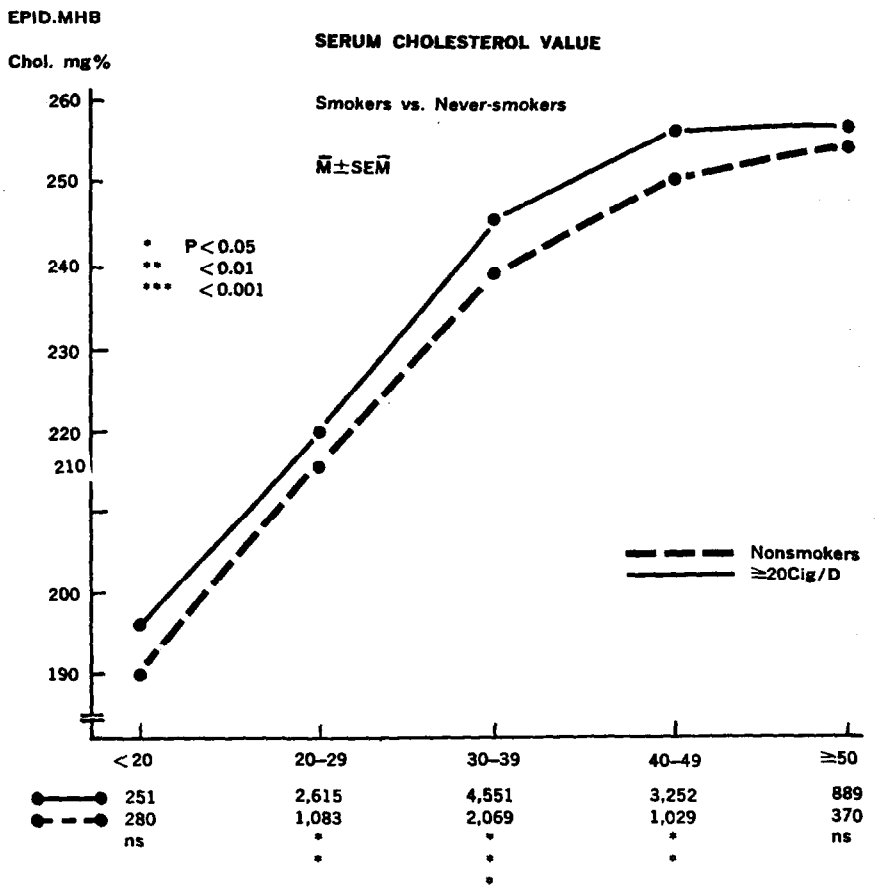

FIGURE 3.—Serum cholesterol levels of cigarette smokers and nonsmokers in the Belgian military service.

SOURCE: Van Houte, O., Kesteloot, H. (*CV 33*).

In a prospective study of 10,000 male Israeli civil service workers, aged 40 and up, Kahn, et al. (*CV 22*) found a positive relationship between smoking habits at the start of the study and the incidence of hypertension over a 5-year follow-up period ($P < .01$).

THROMBOSIS

The role of cigarette smoking in promoting thrombosis has not been well defined. Hawkins (*CV 19*) conducted experiments on platelet functions of 30 healthy men and found that the biphasic electrophoretic mobility change of platelets was altered immediately after smoking and returned to normal at 15 minutes.

Whole blood coagulation ($P < .05$), rates of initial clot formation, maximum clot tensile strength ($P < .05$), and clot retraction were all altered in the smokers in the direction of favoring hypercoagulability as compared with nonsmokers, but were not altered further in the smokers either immediately or 15 minutes after smoking one cigarette.

SUMMARY OF RECENT CARDIOVASCULAR FINDINGS

1. Data from recent epidemiologic studies suggest that cigarette smoking acts independently of and in conjunction with certain cardiac arrhythmias to increase the risk of mortality from coronary heart disease in men. Smokers also have a greater probability of dying from CHD at an earlier age than nonsmokers.
2. New epidemiologic data suggest that women who smoke cigarettes have a greater risk of sudden death from CHD than do nonsmoking women.
3. The results of experimental studies demonstrate that the elevated levels of carboxyhemoglobin frequently seen in smokers may result in significantly decreased cardiac work performance and precipitation of ischemic electrocardiographic changes and arrhythmias in patients with clinical and subclinical CHD. Carboxyhemoglobin levels may be of value in determining a person's risk of developing arteriosclerotic cardiovascular disease.
4. Findings from experimental studies confirm that nicotine acts indirectly to cause elevations of plasma FFAs. The relative role of sympathetic versus adrenocortical stimulation of the rise in FFAs remains to be determined.
5. Epidemiologic data reveal strong associations between cigarette smoking and development of peripheral vascular disease.
6. Data from epidemiologic studies support a strong association between atherosclerotic brain infarction and cigarette smoking in premenopausal women and in men of all ages. No association between ABI and smoking has yet been demonstrated in menopausal women.

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CHAPTER 2

CANCER

LUNG CANCER

Introduction

An estimated 72,000 people died of lung cancer in the United States in 1973 (*CA 28*). For males in the age groups 35 to 54 and 55 to 74, cancer is the second leading cause of death, and the lung is the most common site of cancer in these age groups. For men over 75, cancer is the third leading cause of death, and lung cancer trails only cancer of the prostate as the most common cancer in this age group. For women of all ages, lung cancer is now the fourth leading cause of death from cancer, and for both sexes combined, cancer is the second leading cause of death overall.

Cigarette smoking has been identified as the major cause of lung cancer. Epidemiologic, autopsy, and experimental data reviewed in the original Surgeon General's Report and in previous editions of The Health Consequences of Smoking (1967, 1968, 1969, 1971, 1972, 1973) strongly support this causal relationship and are summarized below:

1. A strong relationship between cigarette smoking and lung cancer mortality in men has been demonstrated in numerous prospective and retrospective studies with risks for all smokers as a group ranging from 7.61 to 14.20 times those of nonsmokers.

2. A dose-response relationship between cigarette consumption and the risk of development of lung cancer for both men and women has been demonstrated in numerous studies, with risks in men for heavy smokers ranging from 4.9 to 23.9 times those of nonsmokers.

3. Many investigators in the past have utilized Kreyberg's system of classification of the histopathologic types of lung cancer

(Group I—Epidermoid and oat cell carcinoma; Group II—Adenocarcinoma, bronchio-alveolar cell carcinoma, carcinoid tumor, and mucous gland tumor). The results from many studies in the past have shown a strong association between Group I tumors and cigarette smoking and data from some of these and other studies have revealed an association between adenocarcinoma (Group II tumors) and smoking. However, the association between adenocarcinoma and smoking is not as strong as that demonstrated for Group I tumors, and not all data consistently demonstrate such an association.

4. Although the incidence of lung cancer in women is lower than that for men and data on lung cancer in women are sparse, results from prospective and retrospective studies have demonstrated an association between cigarette smoking and lung cancer mortality in females.[1]

5. The relationships described above have been shown for Caucasian, Negro, Japanese, and Arabic populations.

6. Mortality from lung cancer directly attributable to cigarette smoking is increased in the presence of the "urban factor" and occupational hazards, including uranium mining and exposure to asbestos.

7. The combination of cigarette smoking and occupational exposures to radon daughters in uranium mining or to asbestos have been shown to produce additive and/or synergistic increases in the risk of development of lung cancer.

8. Data from prospective and retrospective studies reveal an increased risk of development of lung cancer in pipe and cigar smokers compared to nonsmokers, but the risk is less than that of cigarette smokers. The differences in mortality from lung cancer between cigarette smokers and pipe and cigar smokers are consistent for differences in inhalation patterns of these two groups of smokers.

9. Dose-response relationships for amount smoked have been demonstrated for pipe and cigar smokers.

10. Evidence has been presented which indicates that cessation of smoking results in a lowered risk of mortality from lung cancer in comparison with the risk of continuing smoking.

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[1] Differences in the incidence in lung cancer of men and women may be explained, at least in part, by differences in numbers of cigarette smokers, amount of daily consumption of tobacco, inhalation patterns, use of filter vs. nonfilter cigarettes, occupational exposure, as well as biologic differences in susceptibility to lung cancer.

11. Results from autopsy studies have shown that changes in the bronchial mucosa which are thought to precede development of frank bronchogenic carcinoma are found more commonly in smokers than in nonsmokers. Many of the studies demonstrated dose-response relationships for these changes.

12. Experimental studies have demonstrated that dogs which chronically inhale cigarette smoke may develop lung tumors. Intratracheal instillation of several fractions of cigarette smoke have resulted in the production of lung tumors in hamsters. Numerous subfractions of tobacco and tobacco smoke have been shown to have skin-tumor promoting activity in mice.

13. Cell and tissue culture studies have demonstrated that constitutents found in tobacco and cigarette smoke condensate (CSC) may produce malignant transformation of tissues, as well as nonspecific changes in cells.

14. Numerous complete carcinogens and cocarcinogens (tumor promoters) have been isolated from and identified in cigarette smoke condensate.

Most of the studies reviewed in the last year confirmed the knowledge of the relationship between cigarette smoking and cancer. A listing of these studies appears in a separate section of the Supplemental Bibliography. A number of studies extended the knowledge of the association between cigarette smoking and cancer, but several studies presented data which were either partially or wholly inconsistent with the known relationships; these two types of studies are reviewed below.

Lung Cancer in Men

Epidemiologic Studies

Tokuhata (*CA 32*) collected data on the families of 270 lung cancer patients and noted familial aggregations for both lung cancer mortality and the cigarette smoking habit. He postulated an autosomal recessive inheritance model for susceptibility to development of lung cancer. However, when the familial aggregation of lung cancer (familial host factor) was controlled for, cigarette smokers still had approximately 5.3 times greater mortality from lung cancer than nonsmokers.

Jha, et al. (*CA 11*) reviewed 25 histologically proven cases of lung cancer in India and found that only 48 percent of the

patients were regular smokers (6 heavy and 6 light smokers). A total of 36 percent of the tumors were adenocarcinoma and large cell undifferentiated carcinoma.

Histopathologic Studies

In an analysis of the 10-year follow-up data from the Philadelphia Pulmonary Neoplasm Research Project, Weiss, et al. (*CA 35*) followed 6,027 men prospectively, including 830 nonsmokers, with semiannual photofluorograms and observed the development of lung cancer in 121 men, 94 cases being proved histologically. All cases of lung cancer occurred among smokers. Analysis of the 67 cases of lung cancer occurring among the 2,580 men who were current smokers at the time of initial observation revealed dose-response relationships for number of cigarettes smoked per day ($P < .01$). Utilizing the WHO criteria for classification of histologic types of lung cancer, the authors found dose-response relationships for smoking and squamous cell carcinoma in toto ($P < .01$), well-differentiated squamous cell carcinoma ($P < .01$), small cell (oat cell) carcinoma ($P < .05$,) and adenocarcinoma ($P < .05$). No dose-response relationship was demonstrated for poorly differentiated squamous cell or large cell carcinoma. The dose-response curve for adenocarcinoma was based on only 14 cases, and for oat cell carcinoma on only 8 cases.

Yesner, et al. (*CA 42*) reviewed 449 biopsies of autopsy-proven cases of lung cancer seen at the Yale-New Haven and West Haven Veterans Administration Hospitals between 1953 and 1959. By utilizing the current WHO criteria for classification of lung cancer, the authors found a considerable number of discrepancies in interpretation and classification of the histologic material between the time of initial diagnosis and the present review of the material. A total of 90 percent of the cases of lung cancer occurred among cigarette smokers; 62.4 percent of the cigarette smokers with lung cancer had either epidermoid or oat cell carcinoma, as compared with 19 percent of the nonsmokers ($P < .001$). A strong relationship was demonstrated between smoking and the development of epidermoid and oat cell carcinomas, but dose-response relationships could not be demonstrated for epidermoid carcinoma. The authors suggested that a reappraisal of associations between specific histopathologic features of lung cancer and smoking may be warranted.

Histopathologic Studies

Kennedy (*CA 12*) reviewed 168 cases of lung cancer in women at the Sheffield Royal Infirmary diagnosed from 1955 to 1971. Smoking information was obtained from 112 charts. In each 4-year interval, there was an increased number of cases of lung cancer compared with the preceding interval, with increases in squamous cell and adenocarcinomas predominating. Unfortunately, changes in the incidence of lung cancer at the Sheffield Royal Infirmary cannot be determined, since the total number of women autopsied during the different time periods was not given. Kreyberg Group I tumors were about 4 times more frequent than Group II tumors in smokers, but only 2.2 times more frequent in nonsmokers. This difference was not statistically significant. After combining the results of this study with those of three other British studies, the author concluded that cigarette consumption ". . . has little influence on the histological appearance of lung cancer in British women." Limitations in the analysis of the data restrict the conclusions which may be drawn from this study, because of confusion in the histologic classification of the cases of lung cancer cited in this article.

Relationships Between Pipe and/or Cigar Smoking and Lung Cancer

Wynder and Mabuchi (*CA 39*) reported on a retrospective study of 30 male patients with lung cancer who smoked exclusively cigars and/or pipes. A control group of current smokers of pipes and/or cigars without smoking-related cancers was matched with the cases for age. The authors found a 2.75 times higher prevalence of Kreyberg Group I tumors than Group II tumors in the lung cancer group. The average age of the pipe or cigar smoking lung cancer patients with Group I tumors was approximately 9 years greater than cigarette smoking lung cancer Group I patients; however, the cigar and pipe smokers began smoking about one decade later than the cigarette smokers. Among pipe and cigar smokers, the lung cancer patients inhaled more frequently than the age-matched controls, but the numbers were too small to draw statistically significant conclusions. The lung cancer group contained relatively fewer individuals who smoked both cigars and pipes ($P < .025$). A dose-response relationship was demonstrated; there was a significantly greater percentage of heavy cigar smokers (greater than 4 cigars per day, $P < .005$) and heavy pipe smokers (greater than 10

pipefuls per day, P <.05) within the lung cancer group than among the controls.

Tidings and Bross (*CA 31*) studied 71 white male cigar/pipe smokers with lung cancer from the Roswell Park Memorial Institute and found no dose-response relationship for cigars, and although the authors stated that no such relationship existed for pipes either, there was a trend toward greater amounts of pipe tobacco consumed in the lung cancer group, especially for more than 10 pipefuls. In neither study did "occasional" cigar smokers appear in the lung cancer group (P <.05).

Secular Trends of Lung Cancer in Women

In an analysis of The U.S. Vital Statistics, Silverberg and Holleb (*CA 28*) projected an 18 percent increase in deaths due to lung cancer in males in 1973 and a 34 percent increase in deaths from lung cancer in 1973 for females compared with 1968 statistics.

Analysis of recent data from Alameda County, California (*CA 1*), confirms this increase in lung cancer incidence among women (figures 1 and 2).

In a review of the national and worldwide statistics on mortality from lung cancer, Schneiderman and Levin (*CA 25*) observed that the mortality rate from lung cancer in men continues to rise, although the rate of rise has diminished over the past decade (figure 3), in concordance with the downward trend in smoking being observed in men (figure 4). On the other hand, the rate of rise in the incidence of lung cancer in women continues to go up (figure 5), resulting in a narrowing of the sex ratio from a high in 1960 to 6.8:1 to a level of approximately 5.8:1 in 1967 (figure 6). The increase in the percentage of women who smoke correlates well with this rising incidence of lung cancer. The male:female mortality ratio is expected to narrow still further, mostly due to the rising incidence of lung cancer in women. The authors stated that the epidemic of lung cancer in women has not yet reached its peak, and if women continue to smoke, the incidence of lung cancer can be expected to rise still further.

Factors Involved in Reducing the Risk of Lung Cancer in Cigarette Smokers

In a series of 88 lung cancer patients, Wynder and Hoffmann (*CA 37, 38*) found that 73 percent of filter smokers and 65 percent of nonfilter smokers with lung cancer smoked more than

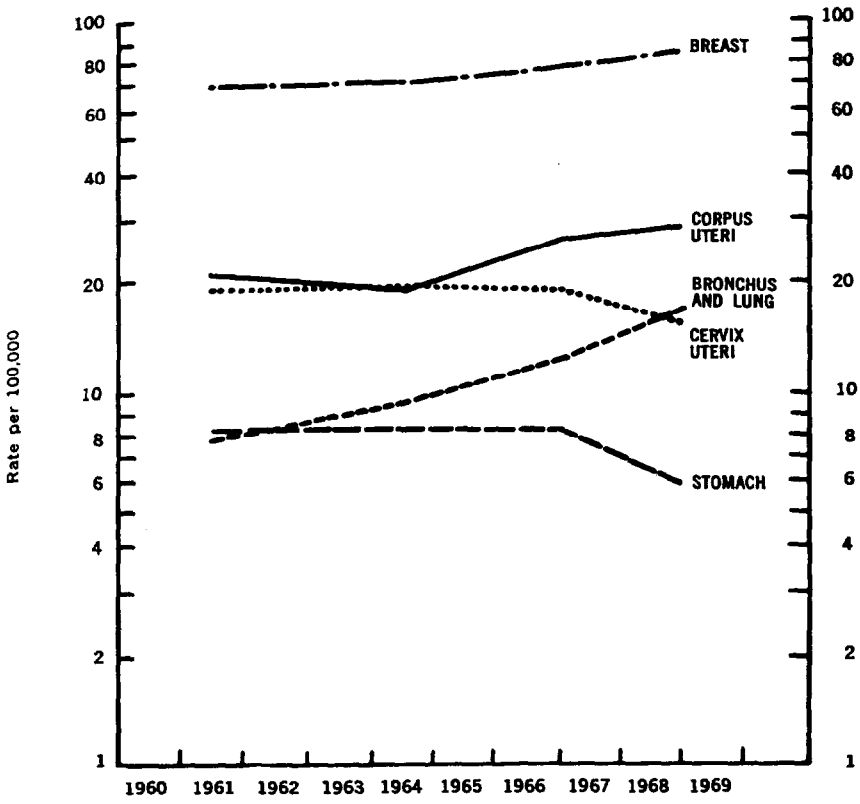

FIGURE 1.—Trends in age-adjusted cancer incidence rates for selected sites (1960–69). White females.

SOURCE: Arellano, M. G., et al. (*CA 1*).

20 cigarettes per day compared to 50 percent of lung cancer patients who smoked similar amounts in 1950. The authors attributed these findings to the reduced amount of carcinogens contained in today's nonfilter cigarettes compared with 20 years ago, and then concluded that the long-term smoker of today's nonfilter cigarettes has a lesser risk of developing lung cancer than the smokers of the nonfilter cigarettes of 1950 (all other measurements of cigarette smoking dosage being equal). Methods of selection of patients were not presented.

Occupational Risks Contributing to the Development of Lung Cancer

In a recent prospective study of 11,656 male members of the Insulation Workers Union in the United States and Canada

whose smoking habits were known (*CA 15*), a dramatic difference was found between the observed and expected incidences of lung cancer among smokers. Among 2,066 men with no history of cigarette use, 2 lung cancer deaths occurred where 5.98 deaths were expected. Among the 9,590 cigarette smokers, 134 deaths due to lung cancer were observed and only 25.09 were expected. These results confirm the synergistic effect of asbestos exposure and cigarette smoking on the risk of development of lung cancer.

In a retrospective study of mortality among 93 female asbestos workers who died between 1960 and 1970 and whose smoking habits were known, Newhouse, et al. (*CA 17*) reported that 16 women died of lung cancer. Fourteen of these women had a history of smoking (87.5 percent), whereas only 65 percent of the total number of deceased women were smokers. This difference is statistically significant ($P < .05$). In a separate publication

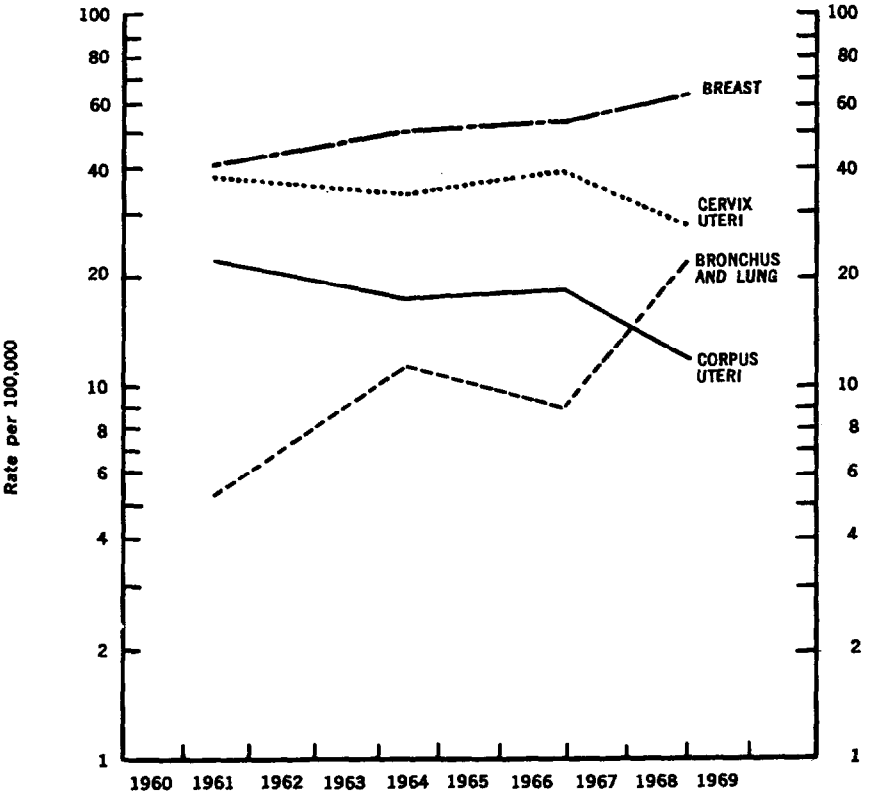

FIGURE 2.—Trends in age-adjusted cancer incidence rates for selected sites (1960–69). Negro females.

SOURCE: Arellano, M. G., et al. (*CA 1*).

(*CA 2*), these workers reported that the interaction of cigarette smoking and asbestos exposure in women, as well as in men, appeared to be multiplicative.

Experimental Studies
Experiments on Humans and Autopsy Material

Heidendal, et al. (*CA 8*) used the Xenon-133 washout technique to detect and localize a clinically and radiographically occult bronchogenic malignancy in one man by observing decreased pulmonary clearance of the radioisotope in the region of the tumor. They then used the same procedure on 10 long-term smokers with chronic coughs but no clinical signs of severe COPD

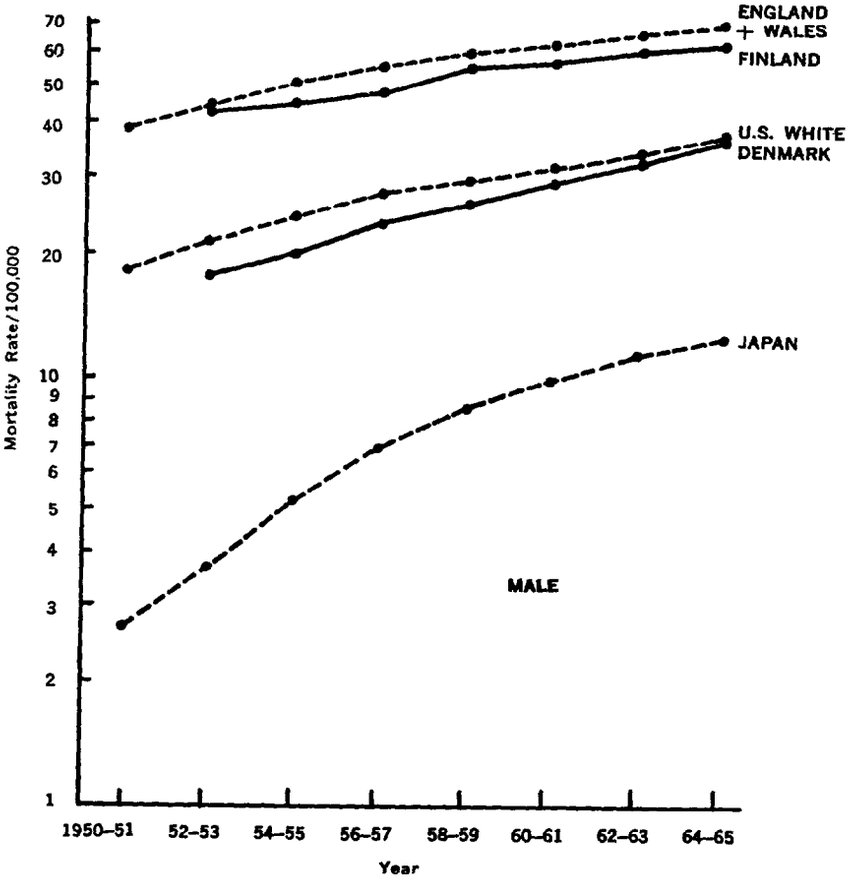

FIGURE 3.—Time trend: Age-adjusted mortality rates from lung cancer (ICD 162 and 163) for men.

SOURCE: Schneiderman, M. A., Levin, D. L. (*CA 25*).

and 10 non or ex-smokers and found no differences in their pulmonary clearance of the radionuclide. The authors felt that the Xenon washout scintiscan may be of use in high risk individuals for the detection and localization of occult lung carcinomas. This technique may be of special benefit to patients with positive or highly suspicious sputum cytologies and negative chest roentgenograms and bronchoscopies.

In an experimental study using silastic casts of the human tracheobronchial tree, Schlesinger and Lippmann (*CA 24*) were able to show that for particles of varying sizes, the mean deposition efficiency of the segmental bronchi corresponded very closely to the distribution of bronchogenic carcinoma in those segments (table 1). The limitations of this experimental model are discussed in detail by the authors.

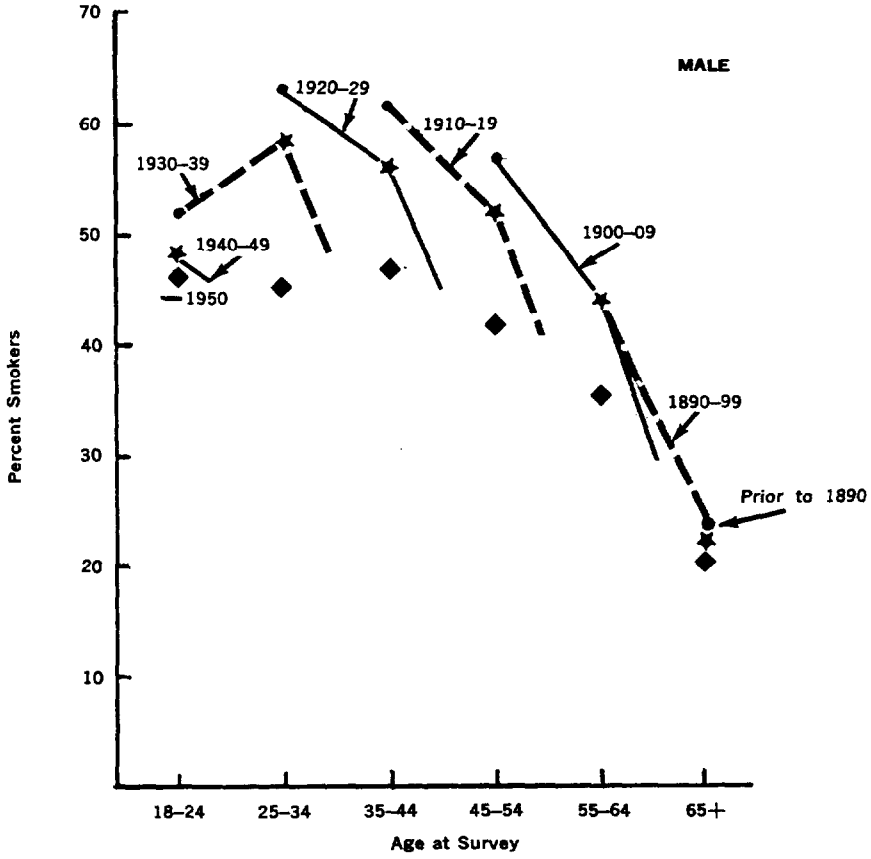

FIGURE 4.—Trends in smoking for U.S. men. Percentage of smokers reported as "currently smoking cigarettes" on surveys taken in 1955 (●), 1966 (★), and 1970 (◆), plotted by age at survey and year of birth cohorts.

SOURCE: Schneiderman, M. A., Levin, D. L. (*CA 25*).

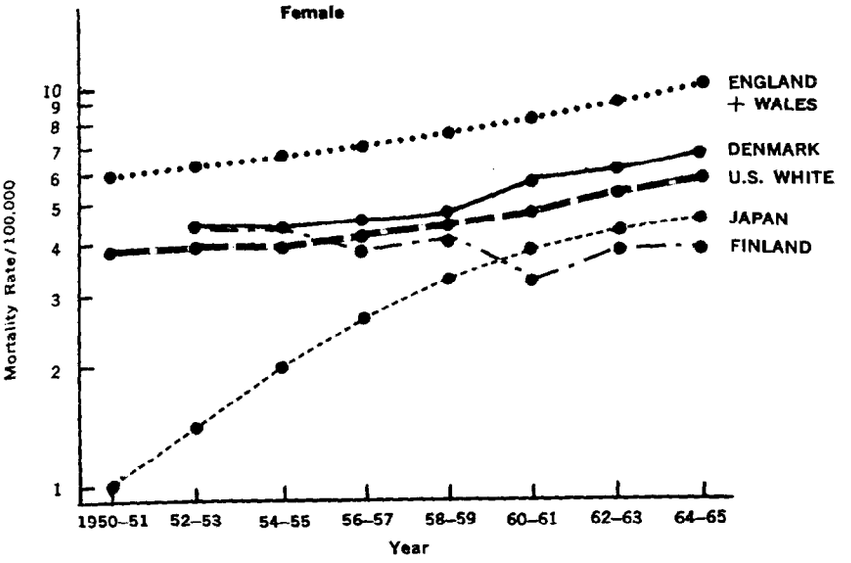

FIGURE 5.—Time trend: Age-adjusted mortality rates from lung cancer (ICD 162 and 163) for women.

SOURCE: Schneiderman, M. A., Levin, D. L. (*CA 25*).

Hoffmann (*CA 10*) has calculated that a heavy cigarette smoker (greater than 30 cigarettes per day) living in a pollutant free environment will inhale from his cigarettes approximately 800 times as much particulate matter (by weight), and approximately 20 times as much benzo(a)pyrene (by weight), as a nonsmoker living in a polluted city environment. The author stated that as much as 95 percent of the pollutant particles and benzo(a)pyrene will be retained within the lungs

TABLE 1.—*Sites of origin of bronchial carcinoma and deposition efficiency for particles in the segmental bronchi*

Lobe Bronchus	Mean Percentage of Total Carcinomas Originating in Lobar Generation which Originate in Each Branch	Mean Efficiency [a] of Each Lobe Bronchus as Percentage of Total Efficiency of Lobar Generation
Right upper	33.5	31.4
Right middle	7.5	6.2
Right lower	19.4	18.6
Left upper	26.0	29.6
Left lower	13.6	14.2

[a] Mean values for deposition efficiency were used because of the range of particle sizes of environmental contaminants which could possibly cause the production of lesions on the respiratory epithelium.

SOURCE: Schlesinger, R. B., Lippmann, M. (*CA 24*).

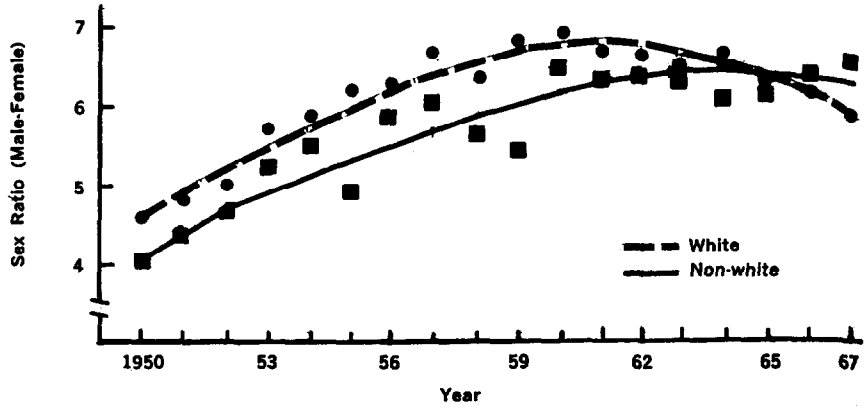

FIGURE 6.—Sex ratio of mortality rates from lung cancer (ICD 162 and 163) for United States.

SOURCE: Schneiderman, M. A., Levin, D. L. (*CA 25*).

of the smoker, while the city dweller retains a smaller fraction of the inhaled material.

Respiratory Tract Carcinogenesis in Animals

In a follow-up study of carcinogenesis of the respiratory tract induced by benzo(a)pyrene and ferric oxide in hamsters, Saffiotti, et al. (*CA 22*) found dose-response relationships for number of tumors per tumor-bearing animal when varying doses of the carcinogen were given in weekly doses intratracheally. Again, the bronchus was the most affected site, and squamous cell carcinoma the most common tumor induced. The latency period for deaths of tumor-bearing animals varied inversely with the tumor dose.

Sellakumar, et al. (*CA 27*), using the same animal model, maintained the concentration of intratracheal benzo(a)pyrene at a constant level, but increased the amount of ferric oxide carrier two and threefold and found no change in the rate of tumor production. Although ferric oxide appears to be necessary for the production of lung tumors in hamsters, particularly when small doses of benzo(a)pyrene are used (the mechanism involves increasing the duration of contact with and the degree of penetration of benzo(a)pyrene into the bronchial and pulmonary tissue), the ferric oxide does not appear to be exerting an independent carcinogenic effect, since no dose-response relationship was noted when the amount of Fe_2O_3 was varied.

In experiments in which benzo(a)pyrene was injected intratracheally into Syrian Golden hamsters weekly for 52 weeks, Feron, et al. (*CA 4*) found dose-response relationships for the

development of respiratory tract tumors, including squamous cell carcinomas of the trachea, bronchi, and bronchiole-alveolar regions. No ferric oxide carriers were employed in this set of experiments. Although squamous cell carcinomas were not the most common tumors produced, they appeared only in those animals receiving the two highest concentrations of benzo(a)-pyrene and in a dose-response relationship. When these results are compared with those from experiments in which ferric oxide was used as a carrier for benzo(a)pyrene, a lower yield of tumors and a longer latency period for the development of tumors were observed. These experiments suggest that ferric oxide need not be present for benzo(a)pyrene to produce lung tumors in the Syrian Golden hamster.

Stanton, et al. (*CA 29*) described a new animal model for the induction of epidermoid carcinomas of the lung. They injected beeswaxtricaprylin pellets intrathoracically in rats and observed that those pellets which contained cigarette smoke condensate (CSC) or the heptane soluble fraction (HSF) of CSC produced epidermoid carcinomas of the lung in 31 of 106 rats. Neither the pellets by themselves nor inclusion of unsmoked tobacco or tobacco ash within the pellets produced this carcinomatous change. The authors concluded that this animal model will be useful for detecting particular carcinogens found in cigarette smoke condensate. The authors stated that, on the basis of their findings, the pulmonary carcinogen(s) found in cigarettes "must be formed and contained in the smoke of the burning cigarette."

Mohr, et al. (*CA 14*) described experiments performed on 10 common European hamsters in which weekly subcutaneous injections of N-diethylnitrosamine resulted in tumors of the nasal cavities, larynx, trachea, and bronchi, including two squamous cell carcinomas of the lung. "Most" bronchi showed metaplastic changes. The two cases of lung cancer were found in the animals who survived to 25 weeks. The authors postulated that if longer survivals were achieved in some of the other animals, more bronchogenic tumors may have been produced.

The Role of Infection in the Development of Lung Cancer

Cigarette smokers have a higher incidence of chronic pulmonary infections than nonsmokers. Cigarette smoking has been shown to be the major cause of chronic bronchitis. However, the possible role of pulmonary infections in the development of lung cancer is less clear, since cigarette smoking is the major cause of chronic bronchitis and lung cancer. The ability of cigarette smoking to contribute to the development of pulmonary infections may also be responsible for some of the effect of

smoking on pulmonary carcinogenesis. Postulated mechanisms include enhancing the repair processes of bronchial epithelial cells, increasing the size of the transformation-susceptible population of cells, disturbing pulmonary clearance of inhaled carcinogens, inhibiting pulmonary immune mechanisms, and enhancing or inhibiting metabolism of carcinogens (*CA 16, 26*).

Nettesheim, et al. (*CA 16, 26*) conducted experiments on the possible influence of pulmonary infection in the development of lung cancer, utilizing several animal models and different infectious agents. They reported that mice exposed to influenza virus in conjunction with smog or $CaCrO_4$ had a reduced incidence of pulmonary adenomas and adenocarcinomas compared to that of mice exposed solely to the pollutants. The acute inflammatory response of the animal to this particular virus may have been responsible for the decreased incidence of tumors in these animals. In a study of rats with chronic murine pneumonia (CMP) (*CA 26*), addition of N-nitrosoheptamethyleneimine (a cyclic nitrosamine) to the rats' drinking water resulted in an increased incidence of squamous cell carcinomas of the lung in male rats, as well as a higher number of tumors per animal in those with CMP compared with uninfected male rats ($P < .005$). For female rats, the dose of carcinogen administered was very high, which may have unintentionally obscured possible differences between infected and uninfected rats. In studies designed to assess pulmonary clearance, these authors found that animals exposed to influenza virus had impaired lower respiratory tract pulmonary clearance. This impairment of clearance was observed acutely and chronically, and may have resulted from entrapment in the inflammatory tissue (acute effect), and from scarring (chronic effect).

The Immune System and Lung Cancer

Pinkerton (*CA 19*) investigated the effect of an experimental animal's immunocompetence on the carcinogenicity of benzo(a)pyrene. After the subcutaneous administration of an adjuvant (Freund's complete, incomplete, BCG, or pertussis vaccine) to pregnant hamsters, there was an enhancement of carcinogenicity of benzo(a)pyrene in the progeny as measured by frequency of skin tumor development and weight of tumor. On the other hand, prior administration of adjuvant to pregnant and nonpregnant female hamsters resulted in diminution of tumorigenesis induced by benzo(a)pyrene in those same animals. The author postulated that induction of tumors by benzo(a)pyrene is influenced by T and B cell activity; in the pregnant and non-

pregnant hamsters in which tumor formation was reduced by treatment with adjuvant, the adjuvant elicited heightened T cell response (cell-mediated antibody) and thus suppressed tumor formation and growth. However, since T cells cannot cross the placenta, a hypothetical humoral substance proliferated by the activated T cells of the pregnant mothers may have crossed the placenta, entered the fetus, and elicited a B cell response (humoral antibody). The author suggested that this humoral antibody may have resulted in increased susceptibility to tumor formation and growth.

Aryl Hydrocarbon Hydroxylase Activity and the Role of Metabolities of Polyaromatic Hydrocarbons in the Development of Lung Cancer

Studies in Humans

Cantrell, et al. (*CA 3*) studied differences in aryl hydrocarbon hydroxylase (AHH) activity of pulmonary alveolar macrophages (PAMs) obtained from 9 healthy smokers and 5 healthy nonsmokers. These investigators found a highly significant increase in AHH activity in the PAMs from the current smokers compared to those of the nonsmokers ($P < .001$). The mean ages and age ranges of the two groups of volunteers were not described, nor were their places of residence (urban vs. rural) stated. In one volunteer, AHH activity within PAMs was observed over a period of time in which he began smoking 10 to 15 cigarettes per day; AHH activity was temporally related to the presence, absence, and duration of smoking in this individual (figure 7). The authors speculated on the role of AHH as a protective mechanism against or, in contrast, as a promoter of carcinogenicity of the inhaled polyaromatic hydrocarbons of tobacco smoke.

Studies in Animals

Welch, et at. (*CA 36*) studied the effect of cigarette smoke inhalation on pulmonary BP hydroxylase (AHH) activity in rats, and reported the following: (1) When rats were exposed to the smoke from 5 cigarettes per hour for 1 to 4 hours, an initial decrease in AHH activity at 1 hour was observed, followed by a substantial increase at 2, 3, and 4 hours (figure 8). (2) This effect was blocked by actinomycin D and puromycin (inhibitors of RNA and protein synthesis) (figure 9). (3) After

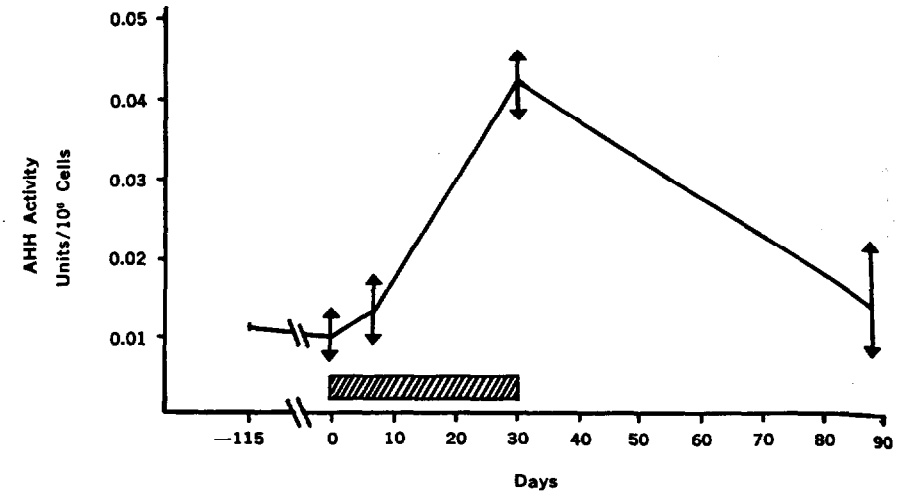

FIGURE 7.—Response of pulmonary macrophages in an individual to cigarette smoking. The shaded bar indicates duration of smoking. The vertical lines indicate the range of duplicate determinations at each time period.

SOURCE: Cantrell, E. T., et al. (*CA 5*).

4 hours of exposure to cigarette smoke, maximal AHH activity was observed at 24 hours (28-fold increase); AHH activity then dropped markedly at 6 days post-exposure, probably owing to the rapid turnover of this enzyme (figure 10) when the inducing hydrocarbons were removed from the lung. (4) In experiments in which the duration of exposure to cigarette smoke was altered, AHH activity increased with increased duration of exposure (figure 11); with as little as a 30-second exposure, at 24 hours a twofold increase in AHH activity was observed. This is in agreement with the observations of Miller and Gelboin, in Gelboin, et al. (*CA 7*), who utilized hamster embryo cells and noted that short exposure to benzo(a)anthracene (2 minutes) resulted in elevations of AHH activity for at least 12 hours. If the metabolites of polyaromatic hydrocarbons are important in pulmonary carcinogenesis, the results of these experiments lend evidence to support the hypothesis that these metabolites would be formed in increased concentrations in the lungs of smokers, and thus would lead to increased risk of tumor formation in smokers. If, on the other hand, the metabolites were noncarcinogenic, the increase in AHH activity may be looked on as a protective device against untoward effects on the parent compound (*CA 34*).

The relationship between pulmonary infection and AHH activity was investigated by Nettesheim, et al. (*CA 16*) who found that at 10 days post-inoculation of influenza virus, AHH activity was reduced in mouse lung tissue to 20 percent of control levels.

Flesher and Sydnor (*CA 6*) reported the synthesis of 6-hydroxymethylbenzo(a)pyrene by incubation of benzo(a)pyrene with rat liver homogenates as a result of enhanced AHH activity. This metabolite was carcinogenic; it produced sarcomas in rats when injected subcutaneously, as did injection of benzo(a)pyrene and 6-methylbenzo(a)pyrene. No control rats were utilized. The authors postulated that methylation and/or hydroxymethylation may be a key step in the metabolism of benzo(a)pyrene, and that the products thus formed may be potent carcinogenic agents in vivo. The fact that 100 percent of the injected rats developed sarcomas, and that no sham treated or solvent injected rats (controls) were utilized, limit the conclusions which may be drawn from this study.

Flaks, et al. (*CA 5*) demonstrated that the 7-hydroxymethyl-12-methyl and 12-hydroxymethyl-7-methyl derivatives of 7,12-dimethylbenz(a)anthracene showed similar carcinogenic potencies to the parent compound. In testing for the carcinogenicity

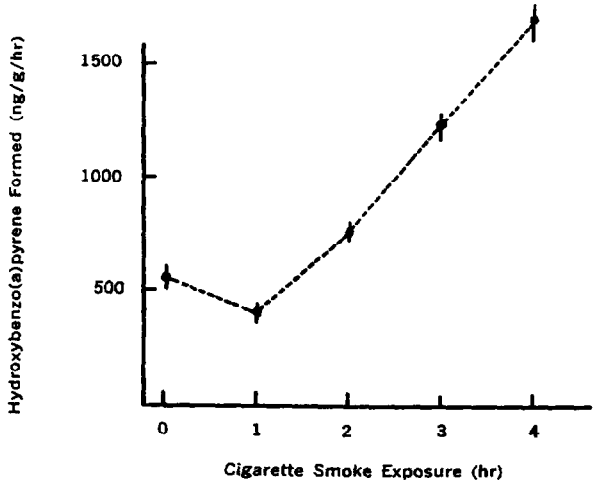

FIGURE 8.—Effect of cigarette smoke on benzo(a)pyrene-hydroxylase activity in rat lung. Four rats were placed in a chamber and exposed continuously to smoke from 5 cigarettes per hour for various time periods. After exposure, the rats were killed and the lungs were examined for benzo(a)pyrene-hydroxylase activity. The data are representative of 4–5 experiments (mean ± SE).

SOURCE: Welch, R. M., et al. (*CA 56*).

of these compounds, these investigators utilized the mouse lung explant experimental model.

Nitrogen dioxide is a known component of cigarette smoke. Palmer, et al. (*CA 18*) found no change in AHH activity of tracheobronchial mucosa of rabbits after exposure to 5, 20, and 50 p.p.m. of NO_2.

ORAL CANCER

Introduction

In the United States, oral cancers comprise approximately 2.5 percent of all cancers reported. These include cancer of the oropharynx, lip, tongue, hard and soft palate, floor of the mouth, gingiva, alveolar mucosa, and buccal mucosa. The relationships of cigarette and pipe/cigar smoking to the development of oral cancer are summarized below:

1. Prospective and retrospective studies have shown an association between mortality for oral cancer and tobacco usage in men and women.

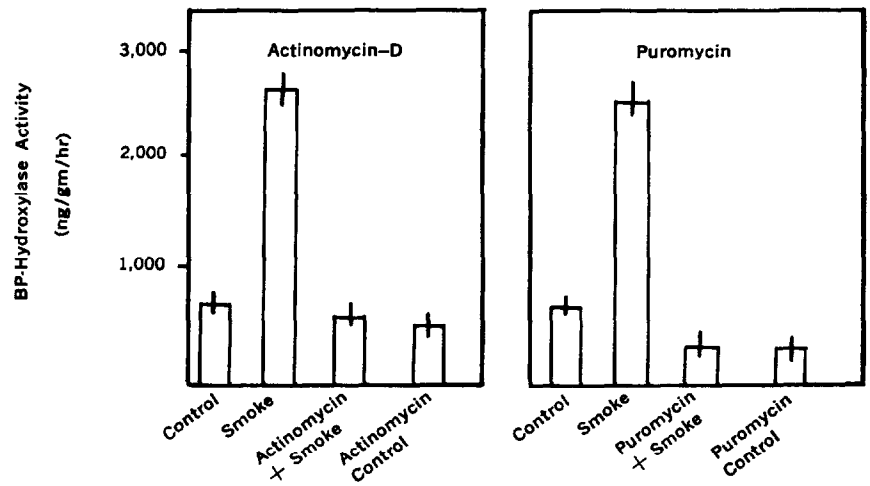

FIGURE 9.—Effect of actinomycin and puromycin pretreatment on the induction of benzo(a)pyrene-hydroxylase by cigarette smoke in the rat. Rats were treated with actinomycin or puromycin and exposed to cigarette smoke for 4 hours. Benzo(a)pyrene-hydroxylase was measured in lung immediately after exposure. Results represent the mean ± SE from 4 rats.

SOURCE: Welch, R. M., et al. (*CA 56*).

2. This association has been demonstrated for all different modes of tobacco usage—cigarette and pipe/cigar smoking, tobacco and snuff chewing, reverse smoking, and "pan" chewing.

3. Several studies have shown that the development of recurrent oral cancers has a highly significant correlation with continued smoking.

4. Tobacco usage may act in concert with alcohol consumption to increase the risk of development of oral cancer.

5. The association between tobacco use and oral cancer in both men and women has been demonstrated for Caucasian, Indian, and Asian populations.

6. Epidemiologic data suggest that premalignant lesions in the oral cavity (e.g., leukoplakia) are associated with tobacco usage.

7. Results from experimental studies indicate that cigarette smoke may contain tumor promoters active in oral carcinogenesis and is a promoting agent in the hamster cheek pouch.

Epidemiologic Studies

In a study of 483 patients with cancer of the mouth and pharynx selected from three New York City VA hospitals, Rothman and Keller (*CA 21*) found that the relative risks of development of

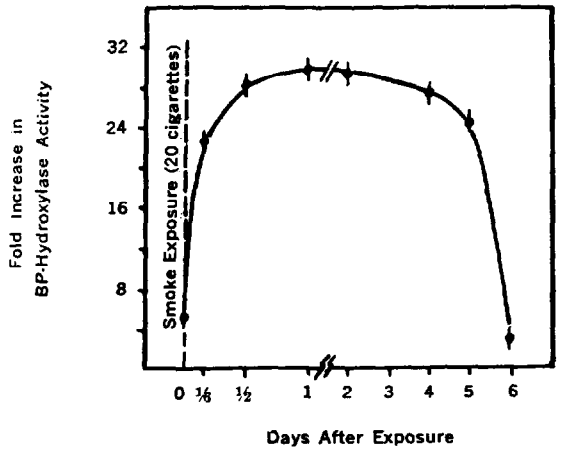

FIGURE 10.—Time course for maximum induction of benzo(a)pyrene-hydroxylase in lung after exposure of rats to cigarette smoke. Rats were exposed to cigarette smoke from 20 cigarettes (4 hours) and killed at various times after exposure. The activity of benzo(a)pyrene-hydroxylase was determined at various intervals after exposure. Each point represents the mean ± SE from 3 rats.

SOURCE: Welch, R. M., et al. (*CA 36*).

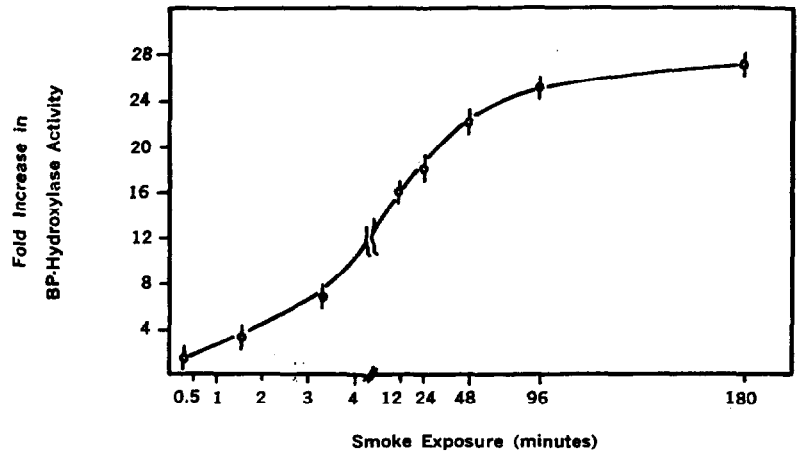

FIGURE 11.—The relationship between lung benzo(a)pyrene-hydroxylase activity and the duration of exposure to cigarette smoke in the rat. Rats were exposed to cigarette smoke from 30 seconds to 180 minutes and killed 24 hours after exposure; the lung benzo(a)pyrene-hydroxylase was measured. Each result represents the mean ± SE from 3 rats.

SOURCE: Welch, R. M., et al. (*CA 36*).

these cancers were higher for men who consumed either tobacco or alcohol than for nonsmokers and nondrinkers. When both tobacco and alcohol consumption were present, dose-response relationships for combinations of the two were demonstrated (table 2). The data presented strongly suggest that both independent and additive effects of tobacco and alcohol consumption were operative in the development of these oral cancers. The authors concluded that the increases in the relative risks of development of these oral cancers produced by smoking and alcohol consumption were additive and, therefore, independent.

Ramanathan, et al. (*CA 20*) examined 407 medical attendants and health workers in Malaysia for evidence of oral precancerous lesions. The authors found significant relations between

TABLE 2.—*Relative risk* of oral cancer according to level of exposure to smoking and alcohol*

		Smoking (cigarette equivalents/day)			
		0	<20	20–39	40+
Alcohol (oz./day)	0	1.00	1.52	1.43	2.43
	<0.4	1.40	1.67	3.18	3.25
	0.4–1.5	1.60	4.36	4.46	8.21
	1.6+	2.33	4.13	9.59	15.5

*Risks are expressed relative to a risk of 1.00 for persons who neither smoked nor drank.
SOURCE: Rothman, K., Keller, A. (*CA 21*).

tobacco smoking ($P < .05$) and mixed habit (smoking, chewing, and/or drinking) ($P < .001$), and the prevalence of oral precancerous lesions in Malay men. Significant differences in the prevalence of oral precancerous lesions were also observed between Indian men with smoking, chewing, and mixed habit and those without these habits. Many oral precancerous lesions were found among women who used tobacco, but the control group of women was too small to make statistically significant comparisons.

Lee, et al. (*CA 13*) retrospectively studied 356 men with squamous cell carcinoma of the oral cavity, matching 316 of these patients with controls of similar age and smoking habits. They concluded that alcohol consumption was significantly correlated with development of oral cancer. They then took 96 of the matched pairs who had similar drinking habits and found no differences in smoking habits.

CANCER OF THE ESOPHAGUS

1. Prospective and retrospective studies have shown a relationship between cigarette smoking and mortality from esophageal carcinoma in men and women.

2. Dose-response relationships have been demonstrated for this association.

3. These relationships have been observed in Caucasian, Asian, and American Indian populations.

4. The effect of cigarette smoking on esophageal cancer mortality rates has been shown to be independent of and synergistic with the effect of alcohol consumption.

5. Experimental data show that benzo(a)pyrene can induce esophageal cancer in mice.

PANCREATIC AND GASTRIC CANCER

1. Data from prospective and retrospective studies of men and women have demonstrated an association between smoking and mortality from pancreatic cancer.

2. Dose-response relationships have been shown for this association.

3. No firm relationship between stomach cancer and cigarette smoking has been established.

Wynder, et al. (*CA 40, 41*), in a retrospective study of 100 men and 42 women with adenocarcinoma of the pancreas, found a significantly higher percentage of male cigarette smokers (P

<.025), female cigarette smokers (P <.05), male cigarette and pipe/cigar smokers (P <.025), and male cigar smokers (P <.025) in the pancreatic cancer group than in the age, sex, and race-matched controls. For male cigarette smokers, a dose-response relationship was demonstrated for numbers of cigarettes consumed in the pancreatic cancer group (figure 12). The number of cases of women smokers with pancreatic cancer was too small to draw statistically significant conclusions with regard to dose-response relationships. Patients who smoked cigars only had a relative risk of 3.1 compared to nonsmokers, and this was also statistically significant (P <.025). (Although the association between cigarette smoking and pancreatic cancer was significant, it was not as strong as the association between cigarette smoking and lung cancer.) Patients who smoked pipes predominantly did not demonstrate a significantly higher risk of development of pancreatic cancer than nonsmokers.

Hirayama (*CA 9*) reported on several previous studies done on Japanese populations. In a retrospective study of 454 patients

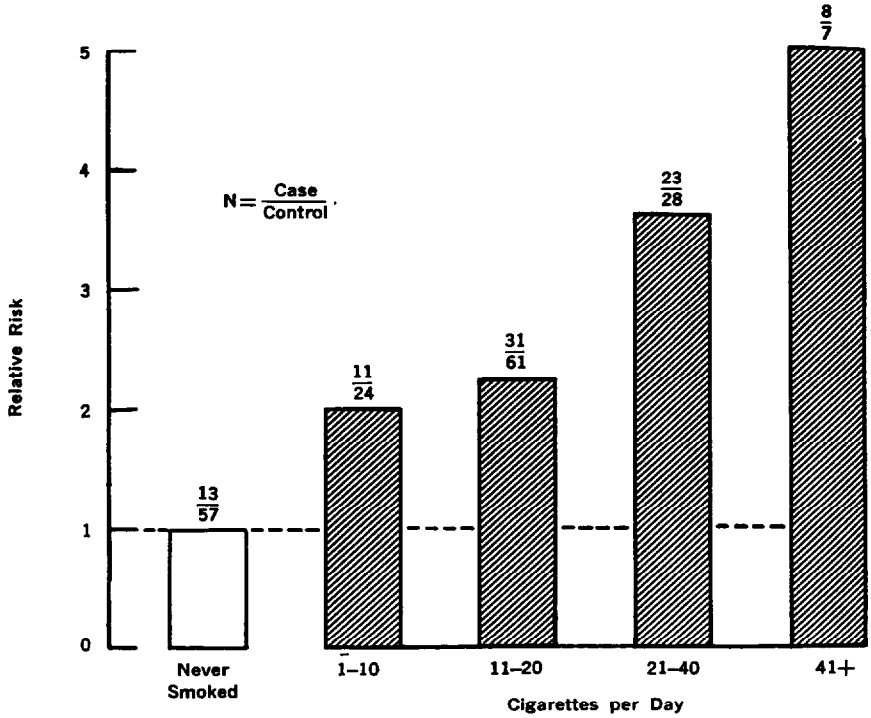

FIGURE 12.—Relative risk of pancreatic cancer by number of cigarettes smoked in males.

SOURCE: Wynder, E. L., et al. (*CA 41*).

with gastric cancer in Kanagawa prefecture from 1960 to 1961, he noted no association between smoking habits and gastric cancer. However, 67 percent of the cases were diagnosed either by X-ray or "clinical methods". In 1963, he studied six prefectures; in 1,524 patients with gastric cancer, there was "no striking association" between smoking habit and gastric cancer. In 1965, Hirayama began his prospective study of 265,118 adults. Analysis of the 3-year follow-up data revealed a higher death rate from gastric carcinoma for males who smoked cigarettes and drank hot green tea. In addition, the age-standardized death rate from gastric carcinoma for male smokers was 128 per 100,000 compared to 85 for nonsmokers; mortality ratios for male smokers:nonsmokers were 1.51. Differences between female smokers and nonsmokers were minimal. The author suggested that, in future studies, a detailed examination of the possible relationships between cigarette smoking and gastric cancer be performed.

CANCER OF THE LARYNX

1. The epidemiologic, autopsy, and experimental data which suggest a strong association between cancer of the larynx and smoking habits have been reviewed in past editions of this report. No new data have been presented within the past year which significantly add to our knowledge of the association between smoking and laryngeal cancer.

CANCER OF THE GENITOURINARY SYSTEM

Introduction

1. The association between cancer of the urinary bladder and kidney and cigarette smoking has been reviewed in previous editions of this report. No new epidemiologic data has been published within the last 12 months which amplifies our knowledge of this association.

2. Data from experimental studies dealing with tryptophan metabolism have demonstrated that metabolites of tryptophan can be carcinogenic in the bladders of mice. These metabolites are found in increased amounts in the urine of patients with non-occupational bladder carcinomas. Some data show an effect of cigarette smoking on tryptophan metabolism, while other data have not shown such an effect.

Epidemiologic Study

Thomas (*CA 30*), in a retrospective study on cytologic and histologic abnormalities of the uterine cervix, reported a significant association between current smoking habits and the incidence of carcinoma in situ ($P < .05$), with a relative risk for smokers being 1.71 ($P < .05$). The "adjusted" risk for smokers was 1.47 times that of the nonsmokers. Intensity and duration of smoking were not analyzed; ex-smokers were also not accounted for. The controls consisted of a hospitalized group of patients with normal cervical smears and may have contained a higher percentage of smokers than the population as a whole. Further epidemiologic studies are needed for full investigation of the relationship between cigarette smoking and development of carcinoma in situ of the uterine cervix, as suggested by this study.

Experimental Studies

Humans

Schievelbein, et al. (*CA 23*) reported no significant differences in the excretion of various urinary metabolites of tryptophan between smokers and nonsmokers, nor between patients with bladder carcinoma (also smokers) and those without this carcinoma. Problems in the design of this study limit the conclusions which may be drawn from the data.

Animals

Wagle and Lee (*CA 33*) found a 2 percent incidence of transitional cell bladder tumors in rats whose bladders were implanted with pellets of cigarette smoke condensate. A total of 23 percent of the rats developed squamous metaplasia.

SUMMARY OF RECENT FINDINGS ON THE RELATIONSHIP OF SMOKING AND CANCER

1. Recent epidemiologic evidence confirms the finding that cigarette smoking is the major cause of lung cancer for both men and women.
2. Current evidence suggests that, even in the presence of a possible genetic susceptibility to the development of lung cancer, cigarette smoking remains the major cause of lung cancer.

3. Results from several studies demonstrated a dose-response relationship between smoking and oat cell carcinoma; a major prospective study demonstrated such a relationship for well-differentiated squamous cell carcinoma, oat cell carcinoma, and adenocarcinoma.
4. The current epidemiologic data suggest that the incidence of lung cancer in women continues to rise. The rising incidence of lung cancer in women correlates well with the increasing trends in smoking among women.
5. Present data are conflicting with regard to dose-response relationships for cigar and pipe smokers and the development of lung cancer; the data are consistent for the fact that light cigar smokers are at a low risk of developing lung cancer.
6. Recent data confirm the synergistic effect of asbestos and smoking exposure on the risk of developing lung cancer in both men and women.
7. Results from experimental studies in hamsters continue to demonstrate that exposure to benzo(a)pyrene results in the production of respiratory tract malignancies, especially squamous cell carcinomas.
8. Data from experimental studies in animals suggest that chronic respiratory infections may enhance the carcinogenicity of components of cigarette smoke, as may alterations in the immune system.
9. Current evidence suggests that components of cigarette smoke induce AHH activity in pulmonary macrophages in humans and in pulmonary parenchymal tissue and embryo cells in animals. The role of AHH in tumorigenesis and/or as a host defense mechanism against potential carcinogens is presently unclear.
10. Recent epidemiologic data strongly indicate that cigarette smoking plays an independent role in the development of oral cancer.
11. Recent epidemiologic data confirm the association between smoking and pancreatic cancer.

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CHAPTER 3

NON-NEOPLASTIC BRONCHOPULMONARY DISEASES

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) (defined here as chronic bronchitis and emphysema) accounted for approximately 25,000 deaths in the United States in 1969. In 1970, in the U.S., the combined prevalence of chronic bronchitis for members of both sexes over age 17 was 29.5 per 1,000 population, and for emphysema was 9.8 per 1,000 population. In 1970, persons with chronic bronchitis lost, on the average, 1.4 workdays per year, and those with emphysema lost greater than 5 workdays per year due to disability from these diseases.

Epidemiologic, autopsy, and experimental data presented in previous editions of this report (1964, 1967, 1968, 1969, 1971, 1972, 1973) indicate that cigarette smoking is the primary cause of chronic bronchitis and emphysema. A summary of that evidence is presented below:

1. Results from numerous prospective studies show a markedly increased mortality from COPD for male smokers compared to nonsmokers. There is a limited amount of data dealing with the relationship between cigarette smoking and COPD mortality in women.

2. Dose-response relationships between cigarette smoking and mortality from chronic bronchitis and emphysema were demonstrated in all studies in which dose-specific mortality rates were evaluated. Heavy cigarette smokers ran relative risks of mortality from chronic bronchitis ranging from 3.6 to 21.2 times those of nonsmokers, and relative risks of mortality from emphysema ranging from 6.9 to 25.3 times those of nonsmokers.

3. Data from many studies demonstrate that male and female smokers suffer from symptoms of COPD (including cough, sputum production, and dyspnea) more frequently than do nonsmokers.

4. Of the studies in which dose-specific prevalence rates were examined, strong dose-response relationships between cigarette smoking and symptoms of COPD were generally demonstrated.

5. The relationship between cigarette smoking and COPD mortality has been demonstrated in the United States, Canada, Great Britain, and Ireland; strong associations between cigarette smoking and COPD morbidity have been shown in the United States, Canada, England, Australia, Finland, Sweden, France, Belgium, Hungary, and Japan.

6. Epidemiologic evidence from many countries indicates that, for both sexes, symptomatic and asymptomatic cigarette smokers have greater impairment of pulmonary function than do nonsmokers.[1]

7. Previous evidence indicates that cessation of smoking results in lower death rates from COPD, improved pulmonary function, and a decrease in the prevalence of pulmonary symptoms.

8. Prospective and cross-sectional analyses of data reveal that pipe and cigar smokers have higher mortality rates from chronic bronchitis and emphysema than do nonsmokers, but lower rates than those of cigarette smokers. Pipe and cigar smokers have a higher prevalence of respiratory symptoms than do nonsmokers. The limited data on pulmonary function studies in pipe and cigar smokers are, thus far, inconclusive.

9. Available data suggest that although air pollution may contribute to the prevalence of symptoms of respiratory disease, cigarette smoking is far more important in producing respiratory disease. Cigarette smoking and air pollution may interact to produce higher rates of pulmonary disease than are seen with either factor alone.

10. Certain occupational exposures result in an increased incidence of COPD, but the relationship is not as strong as for cigarette smoking. The combination of certain occupational hazards and cigarette smoking has been observed, in many studies, to result in additive effects on morbidity from COPD. Exposures to cotton fiber, asbestos, and coal dust, in particular, appear to act in concert with cigarette smoking in the development of pulmonary disease. The role cigarette smoking plays in the development of coal workers' pneumoconiosis is unclear at present.

[1] In these studies, the degree of the relationship between smoking and impaired pulmonary function was found to be dependent on the sensitivity of the particular pulmonary function test utilized to detect pulmonary obstruction and/or small airways disease, the age, sex, occupation, place of residence, general state of health, and intensity of the smoking habit of the population examined.

11. A genetically determined protease-deficiency ($alpha_1$-antitrypsin deficiency), inherited as an autosomal recessive trait, is found as a homozygous deficiency in approximately 1 in 3,600 people and as a heterozygous deficiency in approximately 5 to 8 percent of the population. Those with the homozygous deficiency have an increased prevalence of pulmonary emphysema. It is not clear whether cigarette smoking is an important contributor to the premature development of emphysema in people with the homozygous or heterozygous deficiency states. It is also unknown whether nonsmoking heterozygotes are at a greater risk of developing emphysema than nonsmokers or smokers with normal $alpha_1$-antitrypsin activity.

12. Data from most studies implicate cigarette smoking as an important factor in increasing the risk of developing postoperative pulmonary complications.

13. Some data suggest that cigarette smoking may increase the risk of development of spontaneous pneumothorax.

14. Data from pathologic and autopsy studies have demonstrated a dose-response effect of cigarette smoking on the severity of emphysema; pipe and cigar smokers have degrees of emphysema intermediate between those of nonsmokers and cigarette smokers.

15. Goblet cell density and distention, alveolar septal rupture, thickened bronchial epithelium, and mucous gland hypertrophy have been shown at autopsy to be more common in cigarette smokers than in nonsmokers.

16. Experimental data on humans have demonstrated that inhalation of cigarette smoke results in acute impairment of certain parameters of pulmonary function. Overall pulmonary clearance, ciliary function, and alveolar macrophage function have been found to be impaired in smokers as compared to nonsmokers. Some recent data suggest that acute heavy cigarette smoking with deep inhalation may result in increased pulmonary clearance.

17. In animal studies, in vivo and in vitro exposures to whole cigarette smoke (CWS) and several of its components have resulted in impairment in overall pulmonary clearance, ciliary function, and alveolar macrophage function.

18. Experimental data on humans and animals presented in the past suggest that cigarette smoke may impair the function of the pulmonary surfactant system.

Most of the studies reviewed in the last year confirmed the knowledge of the relationship between cigarette smoking and bronchopulmonary disease. A listing of these studies appears in a

separate section of the Supplemental Bibliography. A number of studies extended the knowledge of the association between cigarette smoking and bronchopulmonary disease, but several studies presented data which were either partially or wholly inconsistent with the known relationships; these two types of studies are reviewed below.

EPIDEMIOLOGIC STUDIES

Smoking and COPD

There have been relatively few studies designed to evaluate the association between cigarette consumption and the prevalence of chronic obstructive pulmonary disease (COPD) in elderly populations. In a random cross-sectional study of 487 men and women between the ages of 62 and 90, living in Edinburgh and registered with a practicing physician, Milne and Williamson (*BP 45, 46*) reported that over 73 percent of the women had never smoked compared with 7.9 percent of the men; 62 percent of the men were current smokers (71 percent of whom inhaled), while only 18 percent of the women were current smokers (50 percent inhalers). In both men and women, a higher percentage of smokers had persistent cough and sputum production than nonsmokers ($P < .001$ for men and $P < .01$ for women), but twice the proportion of male smokers had these symptoms than women smokers. A dose-response relationship was demonstrated, since a higher percentage of heavy smokers had these symptoms than lighter smokers ($P < .01$). In men, 12.4 percent of the smokers had persistent cough, sputum, and a recent chest illness; none of the nonsmokers had this combination. For men, significant differences in histories of wheezing and dyspnea were found between smokers and nonsmokers. For women, a significant difference between smokers and nonsmokers was demonstrated only for wheezing ($P < .05$). The authors found that the FEV% (FEV/VC) was below 60 in 32 percent of the men who smoked compared to 6.7 percent of the nonsmokers ($P < .05$). For women, the figures were 9.4 percent and 3.9 percent. This difference was not statistically significant.

In a cross-sectional study of 300 men and women aged 65 and over in Glasgow, Scotland, Caird and Akhtar (*BP 6*) found that among women chronic bronchitis was reported by 11 percent of nonsmokers, 13 percent of light smokers, and 50 percent of heavy smokers. For men, a dose-response relationship was shown for light and heavy smokers, but the small numbers of non-

smokers (5 nonsmokers; 2 with chronic bronchitis) limit the conclusions which can be drawn from the data.

In a retrospective study of 5,438 men aged 40 and over who were current smokers, Rimington (*BP 55*) examined the relationship between the pattern of smoking and the prevalence of chronic bronchitis. He found that for each level of daily consumption of cigarettes, chronic bronchitis was more prevalent among those smokers who kept their cigarettes in their mouths during the entire period of smoking ("droopers") than among those smokers who removed their cigarettes from their mouths between puffs (normals) (table 1). For all levels of consumption, there was a significantly higher prevalence of chronic bronchitis among "droopers" than among normal smokers ($P < .001$). When these values were age-standardized (this was necessary because there was both a higher incidence of bronchitis and a higher percentage of droopers in men over 60 years of age), there was still a higher prevalence of chronic bronchitis among the "droopers" than among the normals, but the statistical significance of this difference was not presented, nor could it be calculated from the data given.

In an analysis of data from Bosnia and Hercegovina in Yugoslavia, Zarkovic (*BP 73*) reported dose-response relationships between depth of cigarette smoke inhalation and prevalence rates for chronic bronchitis, pulmonary emphysema, asthma, cor pulmonale, and clinical and laboratory signs of obstructive lung disease.

TABLE 1.—*Number, percentage, and age-standardized percentage of chronic bronchitics among 5,438 cigarette smoking male volunteers for mass radiography, aged 40 and older, by amount and method of smoking*

	Cigarettes per day							
	1–9		10–19		20+		All	
	D.	N.	D.	N.	D.	N.	D.	N.
Number of volunteers	60	581	134	1,839	266	2,558	460	4,978
Number of chronic bronchitics	22	150	56	552	113	971	191	1,673
Percentage chronic bronchitics	36.6	25.8	41.8	30.0	42.4	37.5	41.5*	33.6*
Age-standardized percentage of chronic bronchitics	33.9	26.0	41.1	32.1	44.1	41.1	41.6	35.1

*P <.001.

D. = "drooping" cigarette smokers. N. = normal cigarette smokers.

SOURCE: Rimington, J. (*BP 55*).

Olziihutag, et al. (*BP 50*) studied the prevalance of chronic bronchitis in Mongolia and found no association between cigarette smoking and chronic bronchitis in urban women, and a negative association in rural women. These authors found close associations between chronic bronchitis and smoking in men. The authors pointed out that chronic bronchitis increased in frequency with age.

Sherman, et al. (*BP 58*) conducted a study in Detroit on 489 working men and women, among whom 459 were employed in the auto industry. All subjects were referred to one physician for evaluation for workmen's compensation. The authors concluded that their data challenged "the traditional view (held) by . . . much of the medical profession that workers' lung and heart diseases are largely caused by cigarettes rather than by workplace poisons." These investigators studied various occupational exposures within the auto industry and found that both in exposed and unexposed working populations, approximately the same percentages of cigarette smokers and nonsmokers suffered from bronchitis, emphysema, and heart disease. Imprecise smoking histories and the absence of adjustment for several potentially confounding variables limit the conclusions which can be drawn from these data.

The Effects of Smoking on Pulmonary Function in Patients with COPD

In a retrospective study of 41 hospitalized cigarette smokers with a diagnosis of pulmonary emphysema, Lepine and Myre (*BP 37*) found dose-response relationships between number of daily cigarettes smoked and years of dyspnea, years of cough, and impairment of the maximum expiratory flow rate (MEF). No dose-response relationships were found for the presence of cor pulmonale by ECG, X-ray evidence of cardiomegaly, impairment of carbon monoxide diffusion, functional residual capacity, arterial blood gas abnormalities, or the ratio of residual volume to total lung capacity (RV/TLC).

In a retrospective analysis of pulmonary function tests (PFTs) of 140 patients with emphysema, chronic bronchitis, or both, Kass, et al. (*BP 31*) found no correlation between the severity of impairment of pulmonary function tests and the amount or duration of cigarette smoking.

The Effects of Smoking on Pulmonary Function in Healthy Populations

Grimes and Hanes (*BP 24*) studied 1,059 employees of a large insurance company and found that cigarette smoking was associ-

ated with decreases in FVC and FEV_1 for all age groups in men. In women, the younger ex-smokers had higher values on pulmonary function testing than the nonsmokers. Higgins and Keller (*BP 26*), utilizing data obtained from the Tecumseh Study, did note differences in FVC, FEV_1, FEV_1/VC, and $MEF_{50\%}$ between smokers and nonsmokers for both sexes and between smokers of greater than and less than 20 cigarettes per day. In this study, smokers of either sex had lower mean FVC, FEV_1, FEV_1/FVC, $MEF_{50\%}$, average flow during the middle half of expiration ($MMEF_{25\text{-}75\%}$), average flow between 0.2 and 1.2 liters of expiration ($MMEF_{0.2\text{-}2L}$), and peak expiratory flow rate (PEF) than nonsmokers, and all these values decreased with increasing tobacco consumption.

Krumholz and Hedrick (*BP 33*) studied pulmonary function in 91 cigarette smoking and 136 nonsmoking "healthy" male executives, aged 35 to 64. They found significant impairment in the smokers for VC ($P < .01$), FEV_1 ($P < .001$), FEV% ($P < .001$), $FEV_{25\text{-}75\%}$ ($P < .001$), Raw (airway resistance) ($P < .05$), MVV ($P < .05$), RV/TLC ($P < .05$), CO diffusion (D_LCO) ($P < .001$), and $D_LCO/TLC\%$ ($P < .001$). Mean lung volumes were the same in the two groups except for RV/TLC. The methods of selection of patients for this study were not detailed.

Brooks and Waller (*BP 2*), in a study of 2,703 people attending a public health exhibition, found a nonsignificant difference in peak flow rates between smokers and nonsmokers age 45 and over; no differences were demonstrated for the younger than 45 age groups. The authors pointed out a number of biases which limit the conclusions which may be drawn from these data.

Coleman, et al. (*BP 11*) investigated the maximal oxygen consumption (physical work capacity) of 78 members of the Texas Tech University faculty and found no difference in this value between smokers and nonsmokers. However, as the authors pointed out, the mean age of the smokers was seven years less than that of the nonsmokers, and the daily activity level of the smokers was also greater than that of the nonsmokers. The combination of these two effects may have partially accounted for the lack of difference in maximal physical work capacity between the smokers and nonsmokers in this study population.

In a cross-sectional study of men and women from the Western Highlands District and Trobriand Islands in New Guinea, Woolcock, et al. (*BP 70*) found a greater decrease of FVC, FEV_1, and PEF with age in men who smoked compared to nonsmokers (no P value reported). No such differences were found for women for FEV_1 and PEF.

Woolcock, et al. (*BP 69*) also reported that in this same group

of New Guineans smoking was not strongly associated with cough on a single examination in the Western Highlands District (WHD) population, but was strongly associated in the Trobriand Islands (TI) population. The authors stated, though, that the TI population smoked western cigarettes, whereas the WHD population smoked predominantly home-grown tobacco rolled in newspaper and smoked as cigars.

The Roles of Smoking and Pollution in the Development of COPD

Cigarette smoking is the predominant factor in the development of chronic nonspecific respiratory disease (CNRD), but there have been few prospective studies on the interaction between air pollution and cigarette consumption as risk factors in the development of chronic nonspecific respiratory diseases. In an analysis of the initial data from a prospective study of Boston policemen, Speizer and Ferris (*BP 61*) found that a higher percentage of men in three of four smoking categories who worked in areas of heavy traffic had chronic nonspecific respiratory disease compared with men who worked in the outskirts of Boston (figure 1).[1] In general, for each of the four traffic exposure

[1] Criteria for diagnosis of CNRD were those established by the British Medical Research Council Bronchitis Committee (1965).

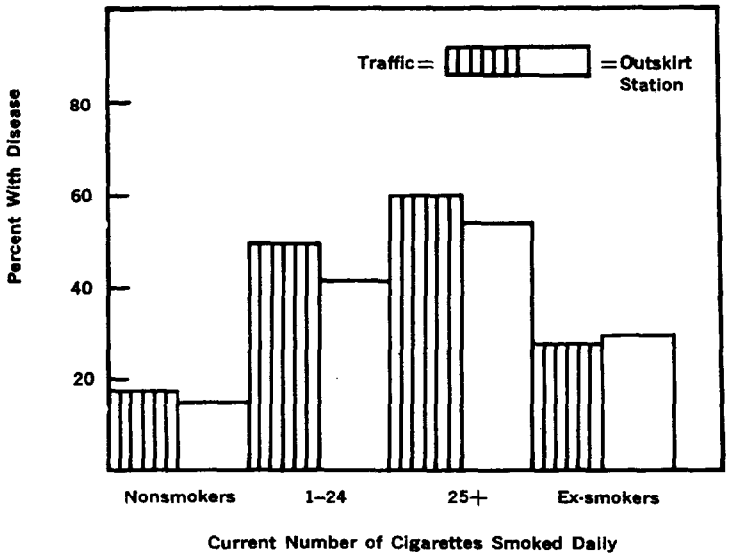


FIGURE 1.—Prevalence of chronic nonspecific respiratory disease by cigarette smoking habits and traffic exposure.

SOURCE: Speizer, F. E., Ferris, B. G., Jr. (*BP 61*).

categories, the prevalence of CNRD was greater among ex-smokers than nonsmokers, and greater among current cigarette smokers than among either ex-smokers or nonsmokers (table 2). Conversely, the prevalence of CNRD in current smokers appeared to be related to the number of years of traffic exposure; those men with few years of such exposure had approximately the same incidence as those who worked in the outskirts. In the analysis of this relatively homogenous group of men, it appears that "traffic pollution" and cigarette smoking may be acting in concert to increase the risk of developing chronic respiratory disease.

TABLE 2.—*Prevalence of chronic nonspecific respiratory disease grouped by current cigarette categories and traffic exposure*

	Total No. Men	Never in Traffic	In Traffic		
			1–10	11–20 yr	20+
Never smoked	45*	11.5	11.1	25.0	16.7
Ex-smoker	86	30.3	27.3	19.0	28.6
Current cigarette smoker	137	49.2	44.1	57.7	64.3
Total	268	36.1	35.2	39.2	39.0

* Never smoked category includes 12 men who have smoked pipe and cigars.
SOURCE: Speizer, F. E., Ferris, B. G., Jr. (*BP 61*).

These authors also measured pulmonary function in this cohort of policemen (*BP 62*) and found correlations between impairment of FEV_1 and lifetime cigarette smoking for all the men ($P < .001$). Statistically significant correlations between impairment of flow volume relationships at 50 and 25 percent lung volume and current cigarette consumption ($P < .05$ and $< .001$), and lifetime cigarette consumption ($P < .01$ and $< .001$) were found for the outskirt station officers, but not for the traffic officers, although the heavier smokers among them did demonstrate impairment of these parameters compared to the nonsmokers and ex-smokers. The data also revealed that the heavier smokers with the longest exposure to traffic had the greatest impairment of flow-volume relationships at 50 percent (and 25 percent) vital capacity, again suggesting the synergistic action of air pollution and cigarette smoking in producing obstructive pulmonary disease.

The Relationship Between Cigarette Smoking and Small Airways Disease

The role of small airways disease in the pathogenesis of COPD has come under close scrutiny in recent years. Results from several studies indicate that the resistance of airways less than 2 mm. internal diameter contributes little to the total measurable pulmonary resistance, and that considerable obstruction of these small airways may be present before changes in the total pulmonary resistance are recorded (*BP 41*). Several techniques have been developed to detect the presence of small airways disease, but some of these are technically difficult, expensive, and impractical for large-scale screening. The measurement of dynamic compliance was one of the first techniques used to demonstrate disease of the small airways (*BP 71*). Patients with small airways disease demonstrate frequency dependent decreases in dynamic compliance compared to controls. More recently, the measurement of closing volume (CV) has been used as a technically easier and less expensive method for the assessment of small airways function. The theoretical basis of these methods in the assessment of small airways disease is described in many recent publications (*BP 3, 4, 5, 10, 20, 23, 25, 28, 34, 36, 40, 41, 42, 43, 63, 66, 71*). It is currently unclear whether those subjects with evidence of small airways disease are particularly susceptible to the development of clinically identifiable forms of COPD.

McCarthy, et al. (*BP 40*) measured closing volumes in 112 subjects by the single-breath argon gas bolus method. Closing volume increased in a linear fashion with respect to age. Of the 66 nonsmokers, no subjects had closing volumes greater or less than 2 SDs from the mean normal values, whereas 26 of 39 cigarette smokers (7 smokers were excluded because of grossly abnormal ventilation distribution as measured by the argon technique) had closing volumes greater than 2 SDs above the mean (figure 2). This difference in closing volume was highly significant ($P < .001$) and indicated a higher prevalence of small airways disease in the group of smokers. Of 14 smokers with abnormalities of standard pulmonary function tests, 13 were symptomatic and all but one had abnormal closing volumes. Of note was that of 17 asymptomatic smokers, 9 had abnormally high closing volumes. Although none of the smokers had sought medical attention, 29 of the 46 smokers had chronic bronchitis, and had, on the whole, higher closing volumes than the asymptomatic smokers.

In a separate publication, McCarthy and Craig (*BP 39*) reported that 15 percent of a group of 91 asymptomatic female smokers in Manitoba had abnormally high closing volumes (CV),

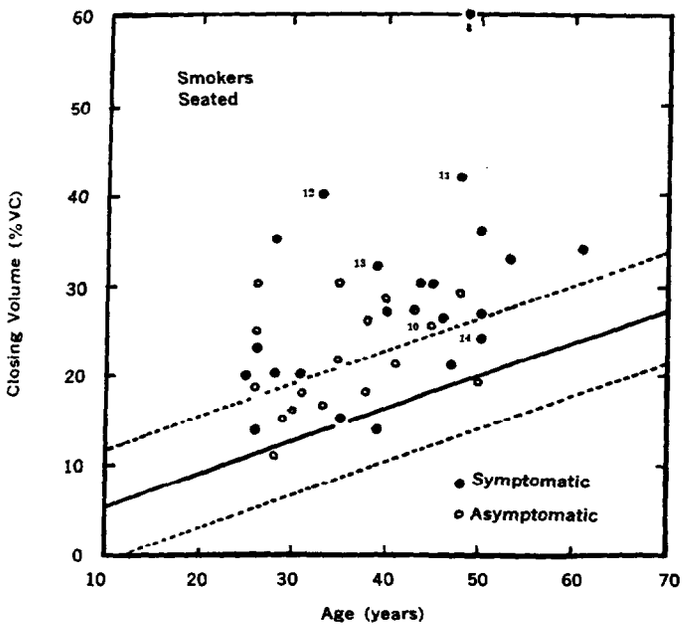


FIGURE 2.—Relationship between "closing volume" and age in 39 smokers. (Thirty-two smokers with normal conventional lung function data and seven smokers whose data are identified by numbers.) Average relationships ±2 SD between "closing volume" and age in sixty-six nonsmokers are also shown. Solid circles indicate smokers who, according to the questionnaire used, had simple chronic bronchitis, and open circles indicate smokers who were asymptomatic. Note that in nine asymptomatic smokers the "closing volume" was above the normal limits.

SOURCE: McCarthy, D. S., et al. (*BP 40*).

in contrast to the 72 percent of 46 male smokers in London (*BP 48*) who had abnormally high closing volumes. None of the female nonsmokers had any CV abnormalities. The authors suggested that differences in pollution exposure of the London and Manitoba study groups might, in part, account for the differences in prevalence of the CV abnormalities.

In a study of pulmonary function of subjects voluntarily reporting to an emphysema screening center, Buist ,et al. (*BP 5*) reported that 6 percent of the nonsmokers, 35 percent of the current cigarette smokers, and 23 percent of the ex-smokers had abnormal CV/VC ratios. In each decade from age 20 to 79, more smokers and ex-smokers had abnormal CV/VC ratios than nonsmokers (figure 3). The daily consumption of cigarettes was related to CV abnormalities in a dose-response relationship for men (figure 4). Among the women, those with a daily consumption of less than 10 cigarettes per day had significantly lower

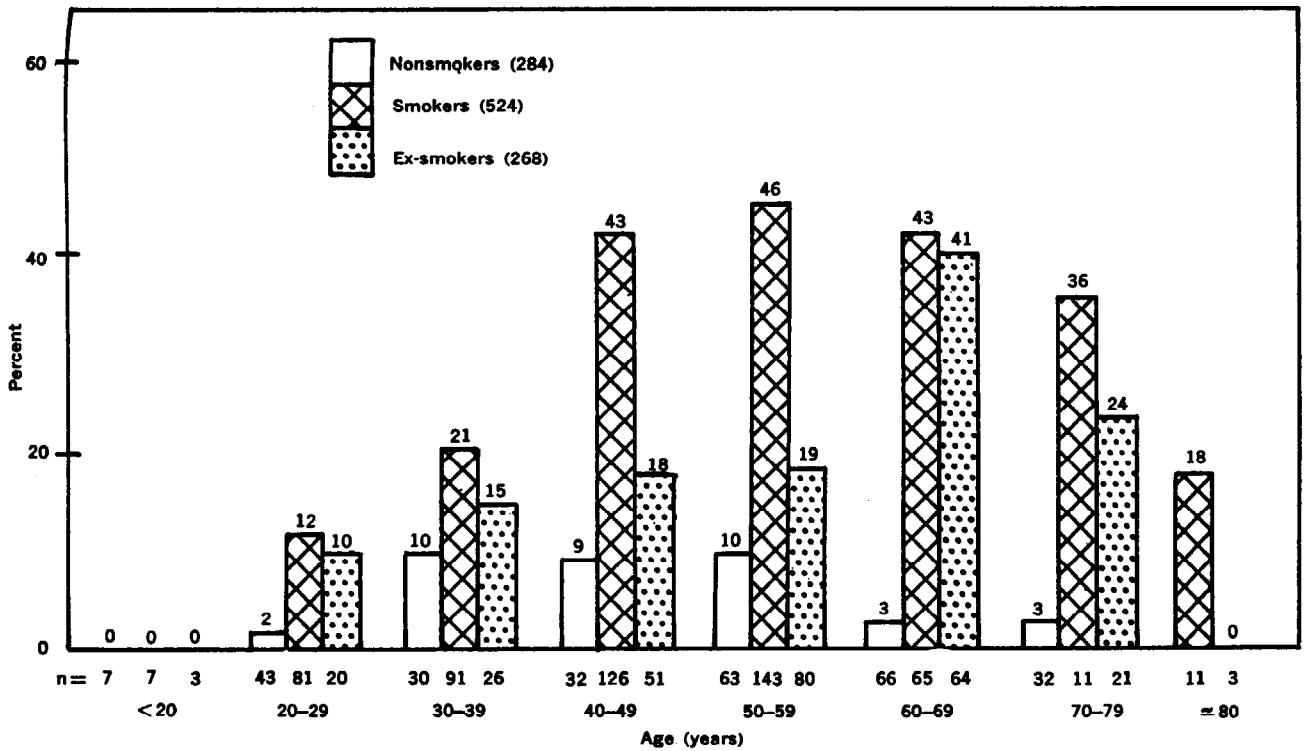


FIGURE 3.—Prevalence of abnormal closing volume/vital capacity ratios in nonsmokers, cigarette smokers, and ex-smokers by age decades.

SOURCE: Buist, A. S., et al. (*BP 5*).

CV/VC ratios than those smoking more than this amount ($P < .05$); but overall, no dose-response relationship was demonstrated (figure 5).

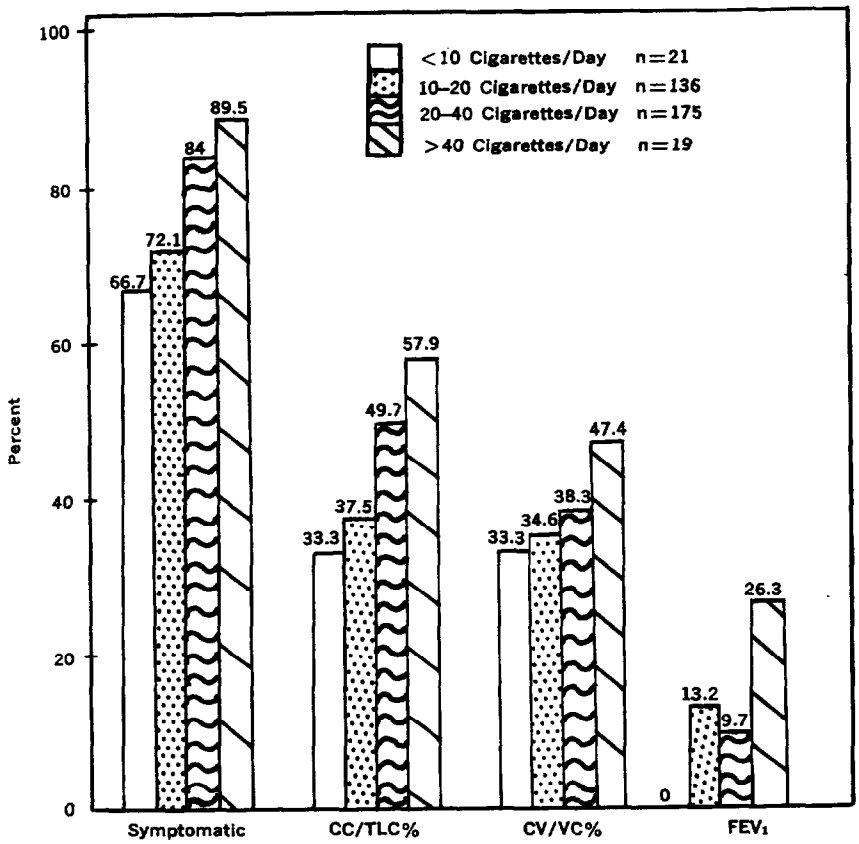


FIGURE 4.—Comparison of the prevalence of respiratory symptoms and pulmonary function abnormalities in male smokers according to their daily cigarette consumption.

CC —Closing capacity
TLC —Total lung capacity
CV —Closing volume
VC —Vital capacity
FEV_1 —One-second forced expiratory volume

SOURCE: Buist, A. S., et al. (*BP 5*).

The Interactions Between Cigarette Smoking and the Genetic Susceptibility to the Development of COPD

Mittman, et al. (*BP 47, 47, 49*) reported on the interaction between cigarette smoking and the genetic susceptibility to development of chronic obstructive pulmonary disease (the $alpha_1$-antitrypsin deficiency state). These authors described the

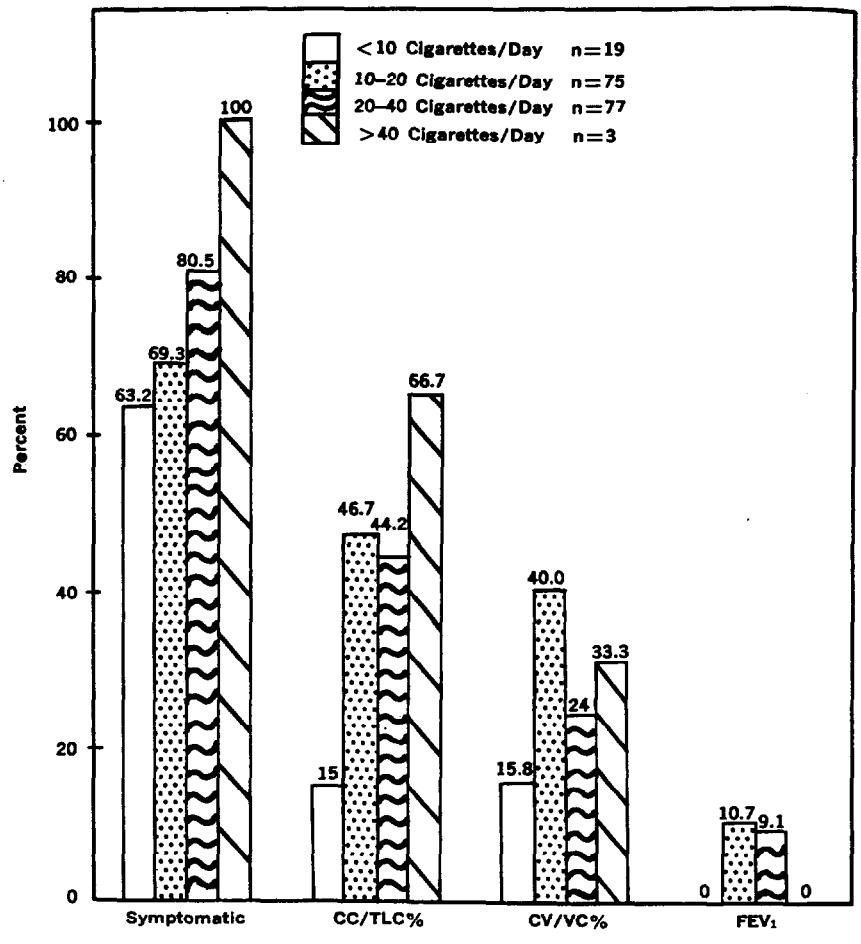


FIGURE 5.—Comparison of the prevalence of respiratory symptoms and pulmonary function abnormalities in female smokers according to their daily cigarette consumption.

CC —Closing capacity
TLC —Total lung capacity
CV —Closing volume
VC —Vital capacity
FEV_1 —One-second forced expiratory volume

SOURCE: Buist, A. S., et al. (*BP 5*).

polymorphic (multiple gene) system of protease inhibition (Pi) by $alpha_1$-antitrypsin (AAT), and listed some of the partial and severe deficiency states of this enzyme system. In a series of 170 consecutive patients with a diagnosis of COPD admitted to the City of Hope Medical Center who had no previously known history of AAT deficiency, 40 patients (24 percent) demonstrated some type of AAT deficiency. This was a significantly higher

percentage than was found in a control group of the Norwegian population, which is known to have a high incidence of this enzyme deficiency ($P < .001$). The lifetime cigarette consumption of the population of patients with emphysema who had an intermediate degree of AAT deficiency was significantly less than those emphysema patients with a normal phenotype (PiMM) ($P < .05$) (figure 6), suggesting a possible interaction between smoking and the genetic abnormality. The data imply that a greater degree of exposure to tobacco was required to produce

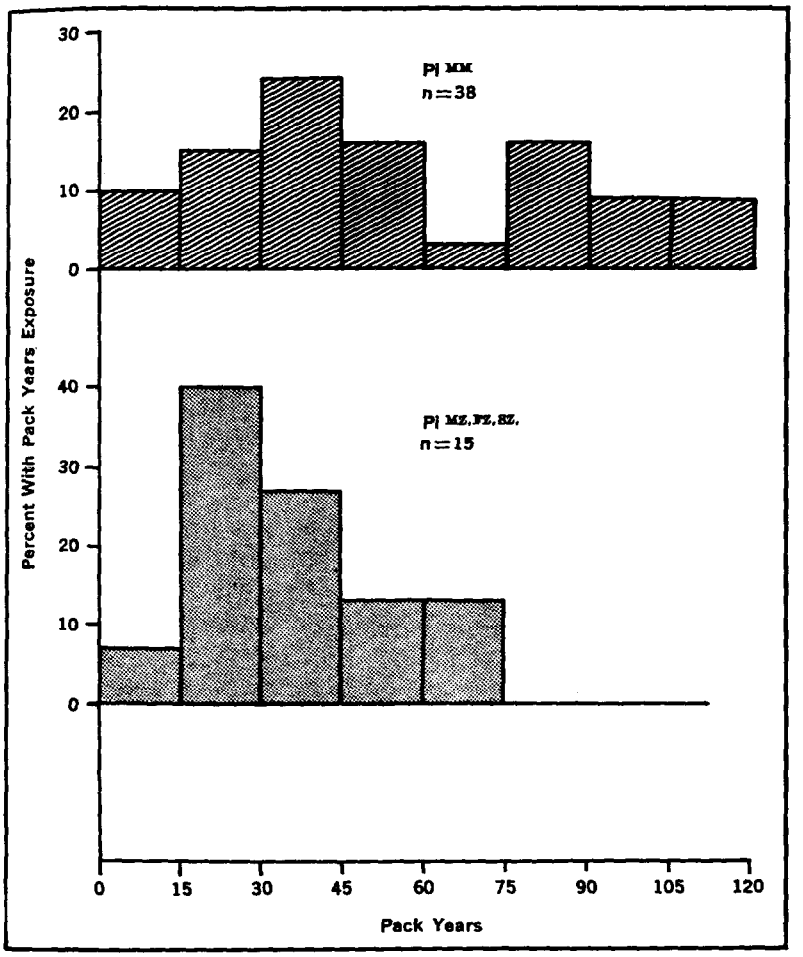


FIGURE 6.—The distribution of smoking histories in men with bronchitis and/or emphysema. Patients grouped by phenotype; Pi ^{MM} patients above, those with intermediate AAT deficiency below. Each bar depicts the fraction of patients reporting smoking histories in the ranges shown.

SOURCE: Mittman, C., et al. (*BP 48*).

emphysema in those patients who did not have a genetic predisposition than in those with the genetic defect. The authors concluded that any degree of AAT deficiency makes an individual more susceptible to the effects of smoking. The same authors have also examined 144 people with partial AAT deficiencies who were apparently healthy and compared them with 100 controls matched for age, sex, and smoking history (*BP 48*). They found that 25 of the 62 smokers with partial AAT deficiency (40 percent) had abnormalities of pulmonary function tests suggestive of obstruction, while 7 of 47 smokers in the control group (15 percent) demonstrated such abnormalities. This difference was statistically significant ($P < .05$).

Hutchison, et al. (*BP 27*) studied 28 patients with pulmonary emphysema, 8 of whom were homozygous deficient for alpha$_1$-antitrypsin. Although the annual consumption of tobacco up to the age of onset of dyspnea was equal in the deficient and nondeficient group of patients, total lifetime tobacco consumption was significantly less among the AAT deficient patients than among the nondeficients ($P < .01$). All 8 AAT deficient patients were smokers. Although there was no significant difference in the incidence or age of onset of chronic bronchitis between the two groups, the AAT deficient group of patients developed exertional dyspnea 12 years earlier than the nondeficients ($P < .001$). These data suggest a synergistic effect of cigarette smoking on the development of pulmonary emphysema in those patients with homozygous deficiency of alpha$_1$-antitrypsin.

Colley, et al. (*BP 12*) analyzed a cohort of 3,899 persons born in the last week of March 1946 in England, Scotland, and Wales and found that irrespective of a history of lower respiratory tract illness before the age of two, the smokers had a greater prevalence of symptoms of winter cough at age 20 than the nonsmokers (table 3). The authors argued that cigarette smoking, by age 20, is a far more important factor in the development of respiratory disease than is a history of lower respiratory tract illness. The results of this study are suggestive evidence against the hypothesis of a purely constitutional susceptibility to the development of respiratory diseases independent of tobacco exposure.

The Effect of Smoking on the Development of Bullous Disease of the Lungs

Stoloff and Victor (*BP 64*) reviewed 44,887 outpatient photofluorograms seen in the Philadelphia Central Mass X-ray Unit from 1969 to 1970, and found 59 men and one woman with bullous disease of the lung. Smoking information was available on

TABLE 3.—*Prevalence (percent) of cough day or night in both sexes in winter by air pollution index, social class, cigarette smoking, and history of chest illness under two years of age.* (Figures in parentheses are population.)*

History of cigarette smoking	Chest illness under 2 years of age	Air pollution index: 7–17, Social class 1 + 2	Air pollution index: 7–17, Social class 3 + 4	Air pollution index: 18–28, Social class 1 + 2	Air pollution index: 18–28, Social class 3 + 4
Never smoked	No chest illness	4.7 (344)	5.7 (369)	4.7 (277)	6.6 (212)
	One or more chest illnesses	12.3 (57)	8.3 (108)	8.3 (84)	10.8 (102)
Present smoker	No chest illness	11.2 (214)	12.6 (325)	14.1 (192)	15.7 (261)
	One or more chest illnesses	16.4 (55)	11.8 (102)	12.3 (73)	22.2 (144)

*Excluding 980 persons—that is, ex-smokers and those whose history of cigarette smoking, social class, air pollution index, chest illness under 2 years of age, and history of cough day or night not known.

SOURCE: Colley, J. R. T., et al. *(BP 12)*.

51 of the men. There were no nonsmokers among the 51 cases ($P < .001$). In nonwhite and white men under age 45 and in nonwhites greater than 45 years old, the rates of this disease increased for each progressively higher level of daily cigarette consumption (table 4). When men without known possible or probable occupational hazards were studied, dose-response relationships were again demonstrated in the nonwhite population, inclusive of all age groups (table 5). The absence of dose-response relations in whites older than 45 may be at least partially explained by the small numbers of cases of bullous disease of the lung found in whites (19 of the 51 cases). The authors stated that the data "are consistent with the hypothesis that cigarette smoke is capable of causing alveolar septal rupture . . ." and, hence, bullous disease of the lung.

TABLE 4.—*Estimated rates of bullous disease of the lung per 1,000 men by age, race, and cigarette smoking habits.*

Race, Sex Age, yr	Nonsmoker	<1 Pack/Day	1 Pack+/Day
WM			
25–44	0	0	1.0
45+	0	4.5	2.9
NWM			
25+	0	4.3	9.9
45+	0	4.1	13.0

SOURCE: Stoloff, I. L., Victor, S. B. *(BP 64)*.

TABLE 5.—*Estimated rates of bullous disease of the lung per 1,000 men with no demonstrable occupational hazard (class 1).*

Race, Sex Age, yr	Nonsmoker	<1 Pack/Day	1 Pack+/Day
WM			
25–44	0	0	0
45+	0	4.0	2.2
NWM			
25–44	0	2.0	5.4
45+	0	4.6	7.7
Total	0	5.2	4.9

SOURCE: Stoloff, I. L., Victor, S. B. *(BP 64).*

Smoking and Post-Operative Complications

Laszlo, et al. (*BP 35*) studied the incidence of post-operative pulmonary complications in 52 bronchitic and 88 nonbronchitic patients undergoing elective surgery in London. They found that a significantly higher percentage of current nonbronchitic smokers (53 percent) developed post-operative pulmonary complications than nonbronchitic nonsmokers (22 percent) ($P < .02$). In patients with no history of chronic bronchitis, there was a dose-response gradient of post-operative bronchitis and/or pneumonia from nonsmokers through ex-, light, and heavy smokers. The presence of bronchitis did not seem to influence the effects of smoking; the bronchitic and nonbronchitic smokers had an equal incidence of pulmonary complications. Of the six cases of severe post-operative bronchitis, five occurred in smokers. The authors noted that each of the three patients who developed severe purulent bronchitis after minor surgery smoked more than one pack of cigarettes per day.

The Influence of Cigarette Smoking on the Development of Pulmonary Disease Associated with Rheumatoid Arthritis

Frank, et al. (*BP 17*) investigated 14 men and 27 women with classical rheumatoid arthritis and evaluated the presence or absence of pulmonary dysfunction in this group. They reported the presence of pulmonary function abnormalities in 57 percent of the men and 33 percent of the women. The men with abnormal pulmonary function tests (spirometry and CO diffusion) had a higher mean lifetime consumption of cigarettes than men with normal pulmonary function tests ($P < .05$); however, the mean age of the abnormal group was 5 years greater than that of the normal group. The women with abnormal values of pulmonary

function tests smoked more than those with normal values (14.44 vs. 9.72 pack years), but the difference was not statistically significant. The group of women with abnormal values was also slightly older than the normal group (by 1.12 years).

Occupational Diseases and Smoking

Byssinosis

Kilburn, et al. (*BP 32*) reported on the prevalence of chronic bronchitis in wool and cotton mill workers in North Carolina. These investigators found that in women the combination of cigarette smoking and cotton dust exposure was associated with a marked increase in the prevalence of chronic bronchitis (figure 7). Of the nonsmoking nonexposed employees, less than 1 percent had chronic bronchitis. Cotton dust exposure and cigarette smok-

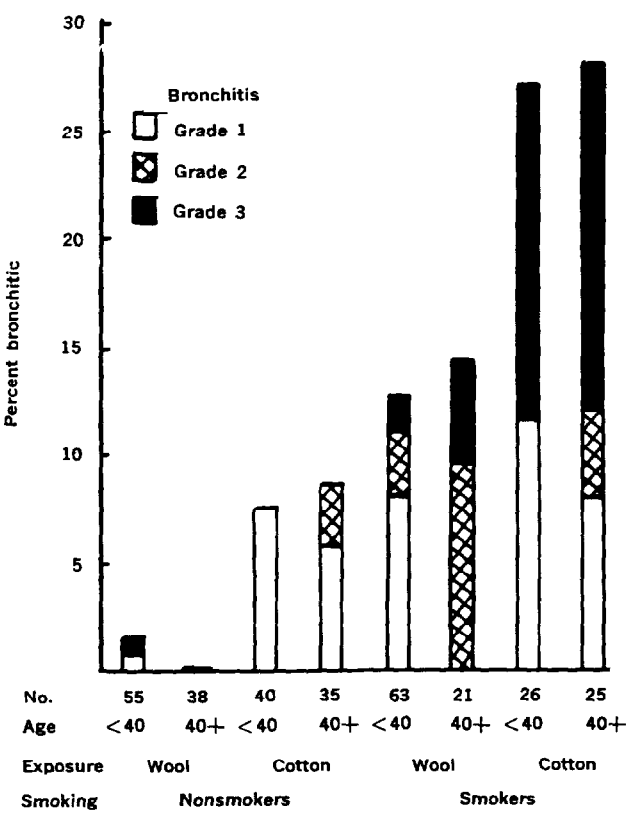


FIGURE 7.—Chronic bronchitis in female wool and cotton textile workers.

SOURCE: Kilburn, K. H., et al. (*BP 32*).

ing alone were associated with prevalence rates of 7 percent and 13 percent, respectively. Both exposures in combination resulted in a prevalence rate for chronic bronchitis of 27 percent. For men, a synergistic effect was demonstrated (figure 8), but it was not as striking as that for women. The authors suggested that the differences in prevalence of chronic bronchitis between men and women, and the differences in the effects of the two noxious exposures in combination may have been due to the fact that men were more heavily exposed to both cotton dust and cigarette smoke than women.

In a cross-sectional survey of 1,140 cotton workers in England, Fox, et al. (*BP 16*) found by regression analysis, that for each level of dust exposure (mg. yrs./m.^{3}) smokers and ex-smokers had lower FEV_1 observed/predicted percent than nonsmokers. The differences in the slopes of these lines were not significant (figure

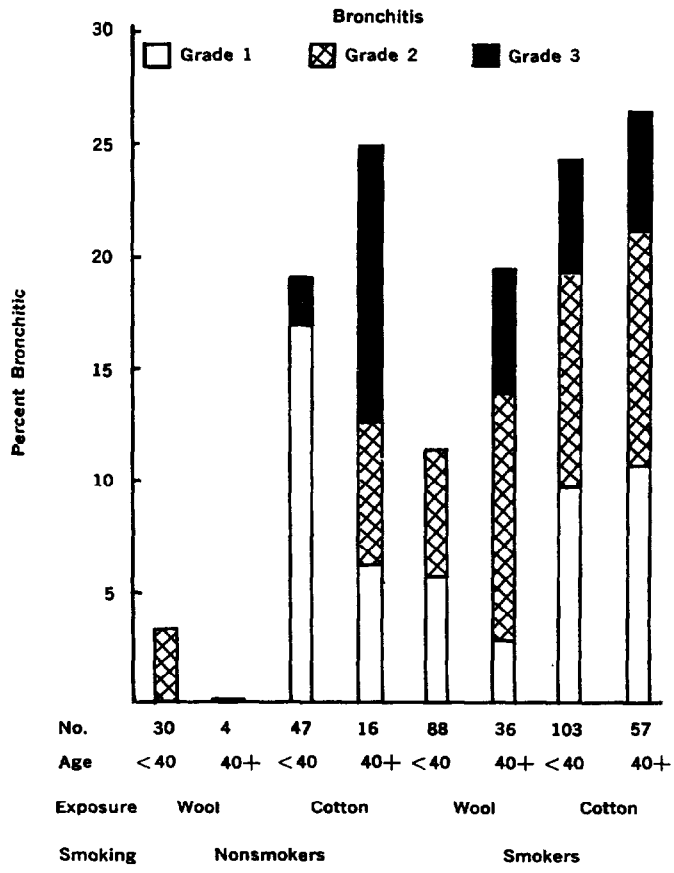


FIGURE 8.—Chronic bronchitis in male wool and cotton textile workers.

SOURCE: Kilburn, K. H., et al. (*BP 32*).

9). The authors also reported that the percentage of smokers with byssinosis was higher than that for nonsmokers at each level of exposure, the slopes of the lines being significantly different ($P < .001$) (figure 10).

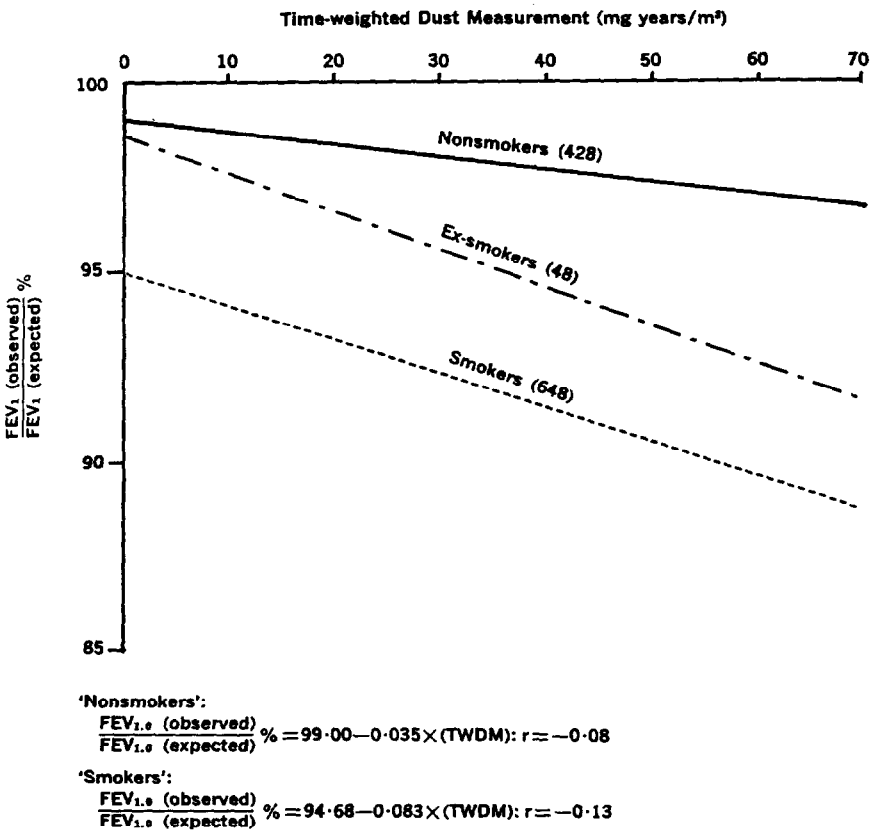


FIGURE 9.—Effect of smoking on pulmonary ventilation (FEV_1) at different levels of time-weighted dust exposure.

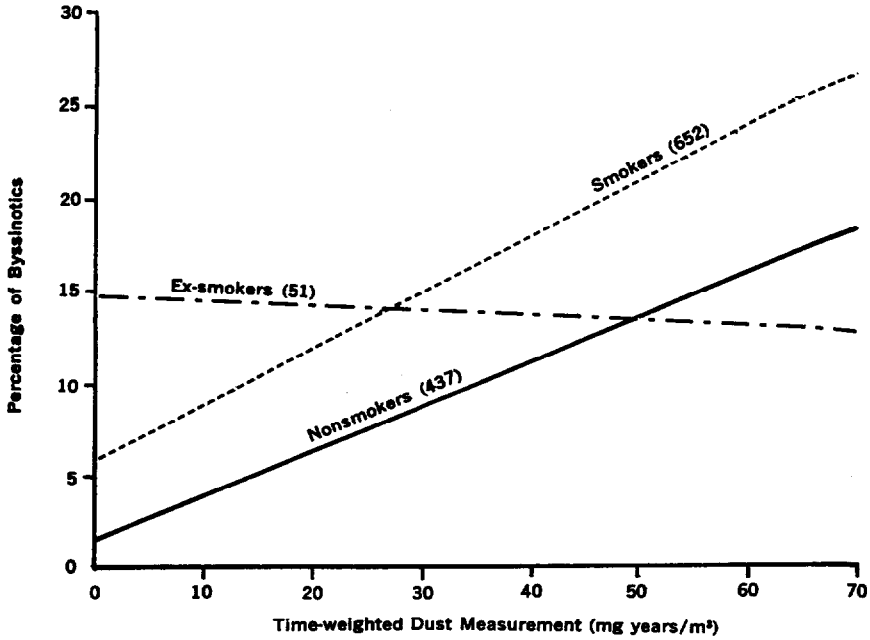
SOURCE: Fox, A. J., et al. (*BP 16*).

Asbestosis

Chew, et al. (*BP 9*) examined 112 asbestos workers in Singapore and found only slight differences in mean FEV_1s between smokers and nonsmokers (2.73 L and 2.79 L, respectively).

Chronic Bronchitis and Pulmonary Symptoms in Cement and Rubber Industry Workers

In a cross-sectional study of 847 cement workers in Yugoslavia, Kalacic (*BP 29, 30*) found that nonsmokers had a higher prevalence of cough, sputum production, exertional dyspnea, and



'Nonsmokers':
%=1·57+0·23×(TWDM): r=0·27

'Smokers':
%=5·76+0·30×(TWDM): r=0·25

FIGURE 10.—Effect of smoking on prevalence of byssinosis at different time-weighted dust exposure levels.

SOURCE: Fox, A. J., et al. (*BP 16*).

chronic bronchitis than controls with other occupations. Within the group of cement workers, cigarette smokers had higher prevalence rates of cough, sputum production, exertional dyspnea, wheezing, and chronic bronchitis than nonsmokers regardless of the number of years of exposure in the cement plants. No significant differences in FVC or FEV% were observed between cigarette smoking and nonsmoking cement workers.

Osman, et al. (*BP 51*) studied 230 rubber industry employees in Egypt and found a higher prevalence of upper respiratory tract irritation, acute bronchitis, and chronic bronchitis in smokers compared to nonsmokers (NS). There was a lower prevalence of these three conditions among control smokers compared with smokers exposed to these industrial fumes, thereby suggesting a synergistic action of cigarette consumption and exposure to rubber industry fumes.

AUTOPSY STUDIES

The Effect of Smoking on the Prematurity of Development and Severity of COPD

Spain, et al. (*BP 60*) evaluated the degree of emphysema in whole lung mounts of 134 victims of accidents, suicide, homicide, or sudden coronary death autopsied at the office of the Medical Examiner of Westchester County (85 men and 49 women). Degree of emphysema was graded from 0 to 100. In men, 3 of 30 nonsmokers had grades of 20 or higher (10 percent), while 16 of 41 heavy smokers had grades of 20 or higher (39 percent). This difference was significant ($P < .01$). The highest grade which the nonsmokers reached was 20, whereas several of the heavy smokers reached grades of 50 (precise data not given). The mean ages of the nonsmokers, light smokers, and heavy smokers with grades 20 or greater were 66, 62, and 52, respectively. The mean grade of emphysema in all the heavy smokers was 14, compared to 11 in the lighter smokers and 8 in the nonsmokers. Among 21 nonsmoking women, there were no cases of grade 20 or greater, while in the heavy smokers 5 of 22 cases had grade 20 or greater. The mean age of this group of smokers was 40. For the women, as in the men, the mean grade of emphysema rose with the intensity of smoking. The authors attributed the differences in degrees of emphysema solely to smoking.

Smoking and Mucous Gland Abnormalities

In an autopsy series in Glasgow of 149 men and women with known smoking histories, Scott (*BP 57*) studied the degree of mucous gland hypertrophy using the Reid index and point-counting technique. He found that the mean Reid index was significantly greater in smokers than nonsmokers ($P < .01$) and that fewer smokers had normal Reid indices than nonsmokers ($P = .02$). Although more smokers had an abnormally high Reid index compared to nonsmokers, the difference was not statistically significant. In this autopsy series, the Reid index was found to be higher in young subjects; also men were noted to have a significantly higher index than women ($P < .05$).

Abnormalities of the Small Airways

Matsuba and Thurlbeck (*BP 44*), in a study of postmortem lung specimens, found that in patients with chronic bronchitis without emphysema who died of nonrespiratory causes, there

was significant narrowing of small airways compared to patients without either chronic bronchitis or emphysema, as measured by the smaller average diameter of the small airways ($P < .001$). These patients had an excess of airways with 0.2 to 0.6 mm. internal diameter and a deficit of airways with an internal diameter of 0.6 to 1.8 mm. (figure 11). In addition, these workers observed more mucus in the airways of the patients with chronic bronchitis without emphysema than in those patients without either disease. The authors concluded that both small airway narrowing and mucus plugging constitute the major morphologic lesions corresponding to the functional abnormalities of small airways seen in patients with chronic bronchitis.

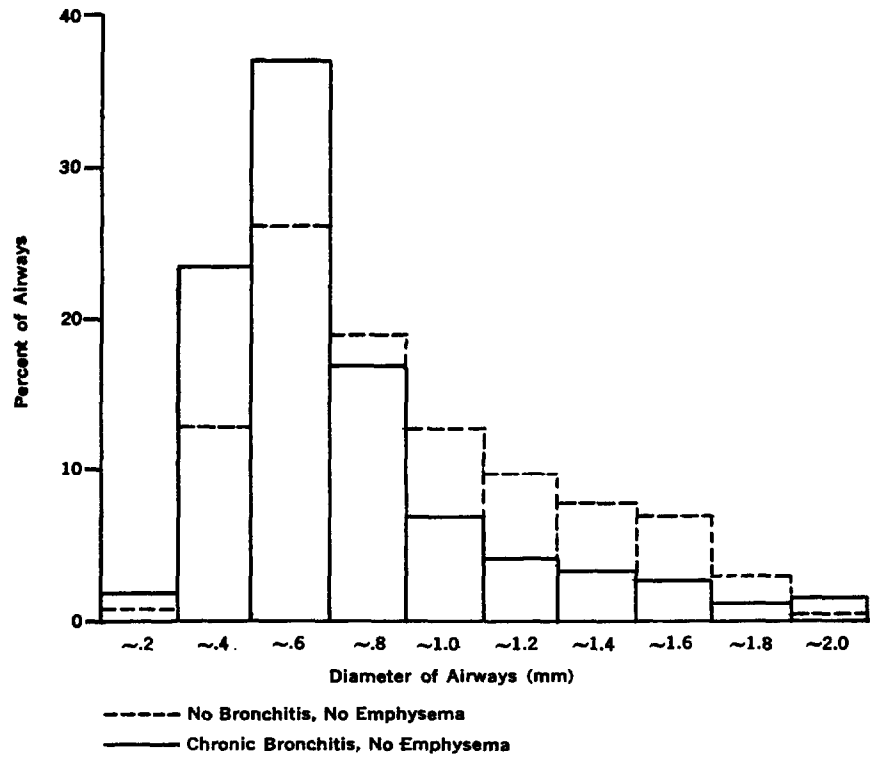


FIGURE 11.—A frequency distribution curve of the internal diameters of the small airways in an autopsy population of nonemphysematous patients with and without histories of chronic bronchitis.

SOURCE: Matsuba, K., Thurlbeck, W. M. (*BP* 44).

EXPERIMENTAL STUDIES

Studies in Humans

Paterson, et al. (*BP 52*) measured pulmonary function in a group of 16 nonsmokers and 10 heavy cigarette smokers before and after exercise. No significant differences in FVC, FEV_1, MMEFR, and FRC were observed between these two groups before exercise. However, after exercise, the smokers exhibited a greater drop in MMEFR, FEV_1, and specific airways conductance than the nonsmokers, thus demonstrating that post-exercise airways narrowing was greater in the smokers. The nonsmokers demonstrated a greater improvement in all these parameters measured after exercise following use of disodium chromoglycate (an anti-bronchoconstrictive agent) than the smokers. The authors suggested that the increase in airways resistance in nonsmokers was mostly due to bronchoconstriction; that seen in smokers was thought to be a combination of bronchoconstriction, mucosal edema, and accumulation of secretory debris.

Using simultaneous helium bolus and nitrogen dilution techniques on 9 subjects, Linn and Hackney (*BP 38*) showed that, with the He method, none of 4 nonsmokers had mean CV/VC % greater than 15.9, whereas both the current cigarette smokers and the one ex-smoker had CV/VC% greater than 21.3. The one pipe smoker had a ratio of 18.9. With the nitrogen dilution technique, the same pattern of abnormalities of the CV/VC ratio in this group of subjects was demonstrated. The highest CV/VC% among the nonsmokers was 17.4, and the lowest among the current, ex-, and pipe smokers was 18.0.

Reintjes, et al. (*BP 54*) studied the acute effects of smoking one cigarette on large airway resistance in a group of 30 young healthy male volunteers (15 smokers and 15 non and ex-smokers), and found that immediately after the smoking of one nonfilter cigarette there was a significant increase in mean airway resistance for both smokers and nonsmokers ($P < .001$). The FEV% did not vary after the smoking of the cigarette in either group of volunteers.

Da Silva and Hamosh (*BP 14*) reported on pulmonary function tests performed on 21 volunteers before and after smoking one nonfilter cigarette, and found that total airway resistance (Raw) was significantly increased ($P < .001$ and $MEF_{50\%}$ was significantly decreased after smoking ($P < .001$). Other measurements, including those used to assess small airways function, showed no significant changes from the control to the post-smoking states.

Stone, et al. (*BP 65*) conducted experiments on 19 volunteers,

4 of whom had chronic bronchitis. There were 11 cigarette smokers and 8 nonsmokers. These authors found that the infusion of isoproterenol increased specific airway conductance (SGaw) equally in smokers, nonsmokers, and patients with chronic bronchitis. Likewise, infusion of propranolol decreased SGaw equally in all these groups of subjects. Alpha-adrenergic stimulation and blockade had no effect on SGaw in any of the experimental groups.

In an experimental study evaluating pulmonary clearance in 79 elderly subjects, Thomson and Pavia (*BP 67*), utilizing $Tc^{99m.}$ labeled polysterene particles of 5μm., found no statistically significant difference in pulmonary (mucociliary) clearance of these particles between smokers and nonsmokers with and without evidence of obstructive and restrictive pulmonary disease. The volume of inhaled particles was controlled in this group of experiments. There was a slight diminution in mucociliary clearance of the healthy smokers compared to the nonsmokers. The group of subjects with impaired pulmonary function had higher clearance rates than the normals, probably owing to the greater deposition of particles nearer the mouth. Among the subjects with subnormal pulmonary function, smokers had slower clearance rates from 1 to 5 hours after inhalation of the particles, but these differences were not statistically significant (figures 12 and

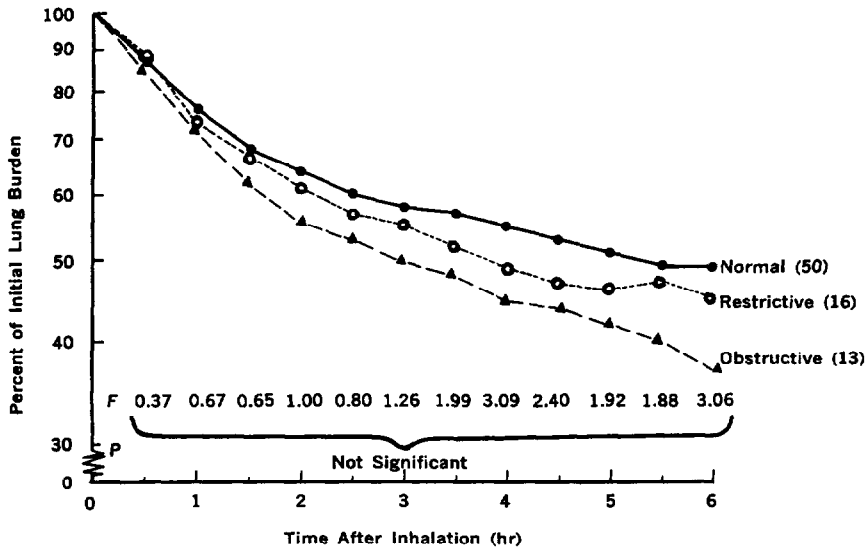


FIGURE 12.—Mean clearance curves for normal subjects, subjects with airway obstruction, and restrictive impairment of the lungs. F=Snedecor's F; the value required for significance here at the 5 percent level is 3.11.

SOURCE: Thomson, M. L., Pavia, D. (*BP 67*).

13). Camner, et al. (*BP 8*) reported on clearance rates in 17 young and middle-aged ex-smokers who had stopped smoking for 3 months. These workers noted that mucociliary clearance of 6 μm. fluorinated ethylene propylene (Teflon 120) particles tagged with Tc^{99m} measured at 2 hours post-inhalation had improved at 3 months post-quitting in 11 of 17 patients. Mean retention of particles was significantly higher prior to stopping smoking than at 3 months ($P < .05$), and also was higher at 1 week post-cessation compared to 3 months post-cessation ($P = .005$). In this study, the volume of inhaled aerosol was not controlled. In addition, coughing after inhalation of the particles was reported to be conspicuously absent or rare, whereas in the Thomson study (*BP 67*), the effect of coughing during the study was not discussed.

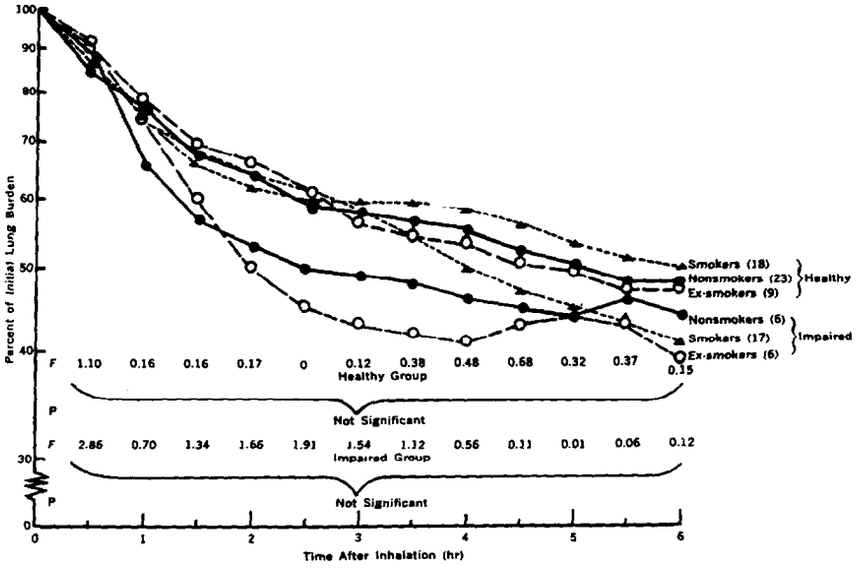


FIGURE 13.—Mean clearance curves for smokers, ex-smokers, and nonsmokers in the healthy group and the group with respiratory impairment. F=Snedecor's F; the values required for significance at the 5 percent level are 3.19 for the healthy group and 3.35 for the impaired group.

SOURCE: Thomson, M. L., Pavia, D. (*BP 67*).

The question of whether the short-term effect of cigarette smoking on enhancing mucociliary transport is specific to cigarette smoke, or is due to a nonspecific reaction of the tracheobronchial tree, was investigated by Camner, et al. (*BP 7*) who found that inhalation of inert carbon particles by 8 normal subjects (including 2 smokers) resulted in similar or enhanced

pulmonary clearance rates compared to the control states. These results suggest that the increased mucociliary transport effected by short-term exposure to cigarette smoke may be a nonspecific reaction.

Westergaard and Olsen (*BP 68*) studied ciliary activity in biopsy specimens from the larynx and carina in 20 patients and found that there was no ciliary activity in epithelial cells from these sites in the entire group of 16 moderate and heavy smokers, while in 3 nonsmokers and 1 cigar smoker normal ciliary activity was observed.

Studies in Animals

Binns and Clark (*BP 1*) described a new experimental model for testing the short- and long-term effects of cigarette smoke on pulmonary physiology. By using male cynomolgus monkeys which were fitted with a specially designed smoking device, these authors demonstrated marked increases in total pulmonary resistance in animals smoking approximately 12 cigarettes per day, for 5 days per week. These changes stabilized at about 20 weeks of exposure and extended through the 6-month test period. The changes in pulmonary resistance were statistically significant ($P < .001$). After 6 months, no changes in tidal volume, respiratory rate, or dynamic compliance were noted. Histologic sections of lungs from smoking monkeys showed clumping of pulmonary alveolar macrophages containing pigmented granules and foamy cytoplasm. These nonspecific cytologic changes have been observed in other animals exposed to cigarette smoke.

Previous editions of this report (1972, 1973) have described experimental evidence concerning the production of emphysematous changes in rat and guinea pig lungs by exposure to nitrogen dioxide (NO_2), one of the gaseous components of cigarette smoke. Freeman, et al. (*BP 18*) described experiments whereby low (10 to 15 p.p.m.), intermittent doses of NO_2 administered over the normal life span of rats resulted in more severe changes of the pulmonary parenchyma than those previously reported; these changes included fibroblastic proliferation, epithelial hypertrophy, loss of cilia in the respiratory bronchioles, fibrosis of alveolar ducts, destruction of alveolar walls, and enlargement of alveolar air spaces. These authors calculated a 29 percent loss of ventilatory surface in the NO_2-exposed rats, occurring in a panlobular distribution. The lungs of the NO_2-exposed rats had greater residual volumes than the controls, and these rats suffered from hypoxemia, hypercarbia, and acidosis, as well as a compensatory polycythemia. Thus, by administering lower doses of NO_2 intermittently, survival of these rats was prolonged (compared with survival of rats receiving continuous NO_2), and the

development of a full-blown picture of emphysema similar to that seen in humans was produced. The relative role of NO_2 in the causation of emphysema in humans is still unknown.

In another series of experiments, Giordano and Morrow (*BP 21*) studied mucociliary clearance rates in female rats exposed continuously to low doses of NO_2 (6 p.p.m.) over a period of 6 weeks. They found a significantly decreased rate of clearance in rats exposed to NO_2 than in nonexposed rats ($P < .02$). In those animals with a decrease in mucociliary activity, the effect of NO_2 was reversible within 7 days following this long-term low dose exposure.

Goldstein, et al. (*BP 22*) reported on the effects of low level NO_2 exposure on bactericidal activity of the mouse lung. They first infected mice with radioactively labelled Staphylococcus aureus and then exposed them to different concentrations of NO_2 for 4 hours. The authors then measured pulmonary radioactivity and bacterial concentrations. They found that at concentrations of 7, 9.2, and 14.8 p.p.m. NO_2 the level of radioactivity was unchanged, but bacterial counts were greater in the NO_2-exposed mice ($P < .05$), and they concluded that the bactericidal activity of the NO_2-exposed animals was significantly less than that of control animals at these concentrations of NO_2. In a series of experiments where mice were first exposed to 1.0, 2.3, and 6.6 p.p.m. NO_2 for 17 hours and then infected with the labelled Staphylococcus aureus, pulmonary bactericidal activity was decreased in the mice exposed to the latter two concentrations of NO_2 ($P < .05$ and $P < .01$). In both sets of experiments, the physical removal rates of bacteria by the pulmonary tree (as measured by the degree of remaining radioactive label) was not influenced by NO_2. These experiments suggest that the retardation of pulmonary bactericidal activity was due to dysfunction of the cellular elements of the pulmonary defense mechanism (i.e., pulmonary alveolar macrophages [PAMs]) in the NO_2-exposed mice.

Fenters, et al. (*BP 15*) exposed four monkeys to low dose NO_2 (1 p.p.m.) for 16 months and infected these animals with influenza virus. Three control monkeys were exposed to the virus, but not to the NO_2. The NO_2-exposed animals had higher hemagglutination-inhibition and serum neutralizing antibody responses against the virus than the nonexposed animals. Pathologic examination of the lungs of these animals demonstrated slight to moderate emphysema in the NO_2-exposed and virus-infected monkeys, along with thickening of the bronchial and bronchiolar epithelium, and no such changes in those animals only infected with virus.

Dalhamn (*BP 18*) conducted experiments on 40 live rats, exposing them to cigarette smoke of different chemical compositions. The cigarette smoke was analyzed for "tar", nicotine, pH, acrolein, nitrogen oxides (NO), acetaldehyde, hydrogen cyanide (HCN), and carbon monoxide (CO). The author found an inverse correlation between the number of puffs required to produce ciliostasis of the tracheobronchial tree and the amount of acrolein, HCN, CO, "tar", and nicotine found in the cigarette smoke. The data appeared to indicate that the majority of the effect was caused by the "tar" and acrolein content of the cigarette smoke.

Gairola and Aleem (*BP 19*) studied the effect of the water soluble and insoluble fractions of tobacco smoke on rat liver mitochondrial function. These investigators found that both fractions were effective in inducing a decline in energy production by the mitochondria, but to differing degrees, thereby suggesting some difference in their mechanisms of action on mitochondria.

Snider, et al. (*BP 59*) exposed rats to 0.1 percent cadmium chloride solution by aerosol, and were able to demonstrate centrilobular emphysema in these animals after 10 days. Since cadmium has been found in cigarette smoke, and smokers and patients with emphysema have been shown to have elevated tissue levels of cadmium at postmortem, further studies defining the role of cadmium in the development of pulmonary emphysema in man would be useful. In Snider's experimental protocol, animals exposed to 1 percent of $CdCl_2$ developed a severe hemorrhagic necrotizing chemical pneumonia, and the lower dose of $CdCl_2$ also elicited a hemorrhagic response, although no evidence of such an inflammatory response was evident 10 days post-exposure.

CYTOLOGIC AND HISTOLOGIC STUDIES

Experimental evidence indicates that cigarette smoke can impair the function of pulmonary alveolar macrophages (*BP 53*). Pulmonary macrophages appear to be the primary defense against bacterial invasion of the pulmonary parenchyma and also serve to remove particulate contaminants from inspired air. In recent experimental work, Powell and Green (*BP 53*) investigated the mechanism of action of cigarette smoke on macrophage function. By using histochemical staining techniques, these workers found that the filtered gas phase of cigarette smoke (FGP) inhibited aldehyde dehydrogenase activity in rabbit pul-

monary alveolar macrophages (PAMs). This effect of FGP was inhibited by prior addition of cysteine to the medium. The loss of enzyme activity correlated with the loss of macrophage phagocytic function (which was also prevented by the prior addition of cysteine). No other enzyme was inhibited by cigarette smoke (except for G6PD in those preparations of cells which adhered to glass). By using crystalline glyceraldehyde 3-phosphate dehydrogenase, the authors demonstrated that FGP inhibited activity of this enzyme, and the degree of inhibition was directly related to the period of incubation (most of the inhibition occurring within the first five minutes). This enzyme was not inhibited by FGP in the presence of cysteine. When enzyme activity was assayed in cell preparations, glyceraldehyde 3-phosphate dehydrogenase activity was reduced by FGP. This inhibition was dose-related to FGP. FGP did not influence G6PD or LDH activity in the pulmonary alveolar macrophages. These experiments suggest that FGP inhibited the glycolytic pathway within the pulmonary alveolar macrophages concurrent with the impairment of phagocytic activity of these cells. The authors postulated that FGP may act as a sulfhydryl agent (thereby explaining the protective effect of cysteine) in the disruption of the activity of glyceraldehyde 3-phosphate dehydrogenase.

York, et al. (*BP 72*) showed that incubation of sheep pulmonary macrophages with tobacco extract resulted in an initial stimulation, then inhibition of macrophage oxygen consumption. When cigarette smoke extract was incubated with the macrophages, a continuous decrease in oxygen consumption was observed, proportional to the incubation period and concentration of smoke extract (figure 14). The enzymatic mechanism of the inhibition of macrophage respiration was not examined in these experiments.

Invertase placed in a medium of calf's serum results in enhanced pinocytosis by sucrose-laden mouse peritoneal macrophages (monocytes). Schwartz, et al. (*BP 56*), utilizing this test system, reported that nicotine inhibited invertase-induced pinocytosis by sucrose-laden mouse peritoneal monocytes by 29 and 18 percent, depending on the concentration of nicotine added to the medium. The contribution of this type of pinocytosis to the bactericidal activity of these monocytes is unclear at present.

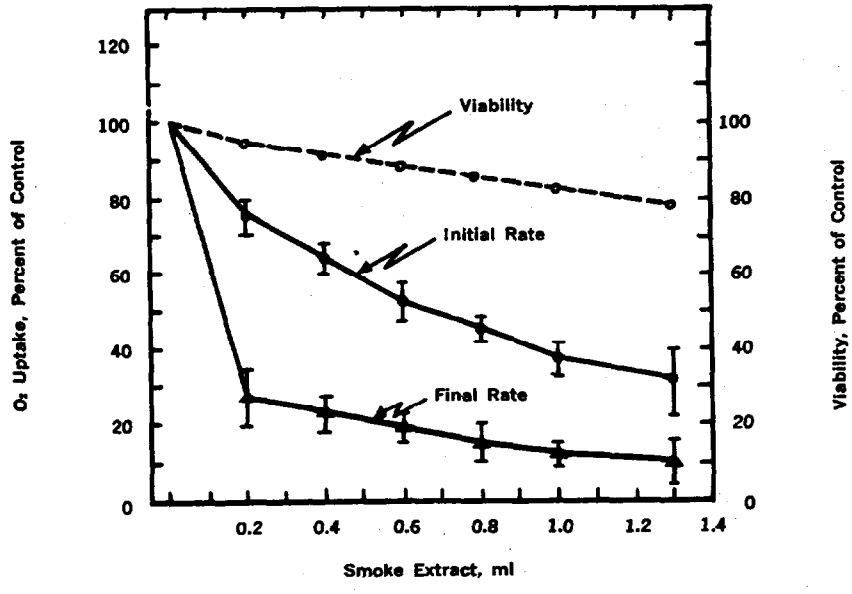


FIGURE 14.—Effects of aqueous cigarette smoke extract on initial oxygen uptake, final oxygen uptake, and cell viability of pulmonary macrophages.

SOURCE: York, G. K., et al. (*BP 72*).

SUMMARY OF RECENT NON-NEOPLASTIC BRONCHOPULMONARY FINDINGS

1. Results from epidemiologic studies on elderly populations demonstrate an increased prevalence of respiratory symptoms and impairment of pulmonary function among smokers of both sexes compared to nonsmokers.
2. Data from several recent studies indicate that standard pulmonary function tests and physical work capacity are impaired in apparently healthy smokers compared to nonsmokers.
3. Recent epidemiologic data suggest that smokers who retain their cigarettes in their mouths continuously while smoking ("droopers") have a higher prevalence of chronic bronchitis than those smokers who remove the cigarette from their mouths between puffs.
4. A recent epidemiologic study confirms the observation that cigarette smoke and air pollution act synergistically in the development of symptoms of respiratory disease.
5. Results from several recent studies indicate that cigarette smokers have a higher prevalence of functional abnormalities of the small airways than do nonsmokers.

6. Results from a recent study suggest that although a history of lower respiratory disease as an infant is related to the prevalence of cough at age 20, cigarette smoking is a far more important factor in the development of cough in young adulthood.
7. Data from a major retrospective study indicate that cigarette smoking is related to the development of bullous disease of the lung.
8. Experimental studies in animals have shown that exposure to nitrogen dioxide, a constituent of the vapor phase of cigarette smoke, results in emphysema-like changes in the pulmonary parenchyma, diminished mucociliary clearance, and impairment of bactericidal activity of alveolar macrophages.
9. Data from experimental studies have demonstrated that the filtered gas phase of tobacco smoke may effect changes in pulmonary alveolar macrophage metabolism through inhibition of the glycolytic pathway; cigarette smoke may also impair oxygen consumption and pinocytic activity of pulmonary alveolar macrophages.

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