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The  
Health Consequences  
of SMOKING

1968 SUPPLEMENT TO THE  
1967 Public Health Service Review

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

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## Foreword

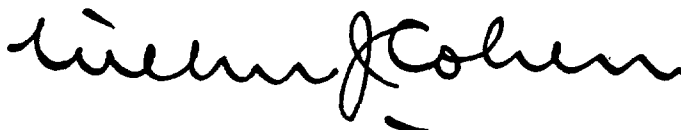
Section 5(d)(1) of Public Law 89-92, the Federal Cigarette Labeling and Advertising Act, requires the Secretary of Health, Education, and Welfare to submit an annual report to the Congress "concerning (A) current information on the health consequences of smoking and (B) such recommendations for legislation as he may deem appropriate." This 1968 Supplement to the 1967 Public Health Service review, "The Health Consequences of Smoking", was prepared for the Secretary pursuant to this section. The Secretary's report was delivered to the Congress on July 1, 1968. It is printed below.

The information presented in the accompanying report, "The Health Consequences of Smoking, 1968 Supplement," confirms or strengthens the conclusions of two previous studies published by this Department—the 1964 Report of the Surgeon General's Advisory Committee on Smoking and Health, and the 1967 Report on the Health Consequences of Smoking.

These conclusions are that smoking is a serious health hazard in this country, one which is bringing about much unnecessary disease and death within our population. In the words of the 1964 Report, adequate remedial action is required. In my opinion, the remedial action taken until now has not been adequate.

I therefore recommend:

1. The warning statement required by the Federal Cigarette Labeling and Advertising Act should be strengthened. This Department would support the wording recommended last year by the Federal Trade Commission, or a suitable paraphrase of the wording.\*
2. This warning should be required to be placed not only on the cigarette package but on cigarette vending machines and in all advertisements.
3. Levels of "tar" and nicotine in cigarette smoke should be published on cigarette packages, on cigarette vending machines, and in all advertisements. Authorization is also needed to make it possible to add other harmful agents to this listing.
4. Appropriations should be made to the Federal Trade Commission to permit the Commission to test all cigarette brands on a quarterly basis for "tar" and nicotine and other harmful agents in cigarette smoke.



Secretary.

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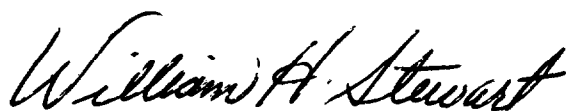
\* The wording recommended by the Federal Trade Commission (Report to Congress, June 30, 1967) was "Warning: Cigarette Smoking is Dangerous to Health and May Cause Death from Cancer and Other Diseases."

## Preface

The following pages provide a review of current information on the health consequences of smoking. As will be seen, the evidence attesting to the harmful effect of smoking on health has continued to mount during the past year, with new research findings confirming the clinical, experimental, and epidemiological relationships between tobacco smoking and many forms of illness related to it. The convergence of research findings continues without substantial negative scientific evidence. New considerations are presented concerning some bio-mechanism involved in the pathogenesis of cardiovascular and bronchopulmonary diseases.

This 1968 Supplemental Report reviews the recent research literature on cardiovascular disease, chronic bronchopulmonary disease and cancer that has become available since *The Health Consequences of Smoking, A Public Health Service Review: 1967* was published. This publication in turn was a review of the research literature which had appeared in the 3½ years since the Surgeon General's Advisory Committee issued its monumental report in 1964. The current research findings should be considered in the perspective of the research evidence previously presented in the 1964 and 1967 reports.

Problems created by cigarette smoking have made this a difficult health issue. Effective preventive programs must be created if we are to meet smoking's grave challenge to human health successfully and reduce the burden of suffering and economic loss involved.

A handwritten signature in black ink, reading "William A. Stewart". The signature is written in a cursive, flowing style with a prominent initial "W".

*Surgeon General.*

## Acknowledgments

The National Clearinghouse for Smoking and Health, Daniel Horn, Ph. D., Director, was responsible for the preparation of this report; Albert C. Kolbye, Jr., M.D., M.P.H., LL.B., was senior editor and David G. Wember, M.D., was staff director.

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# **PART I**

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## **Current Information on the Health Consequences of Smoking**

## Highlights of The Report

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### *General Mortality Information*

Previous findings reported in 1967 indicate that cigarette smoking is associated with an increase in overall mortality and morbidity and leads to a substantial excess of deaths in those people who smoke. In addition, evidence herein presented shows that life expectancy among young men is reduced by an average of 8 years in "heavy" cigarette smokers, those who smoke over two packs a day, and an average of 4 years in "light" cigarette smokers, those who smoke less than one-half pack per day.

### *Smoking and Cardiovascular Diseases*

Current physiological evidence, in combination with additional epidemiological evidence, confirms previous findings and suggests additional biomechanisms whereby cigarette smoking can contribute to coronary heart disease. Cigarette smoking adversely affects the interaction between the demand of the heart for oxygen and other nutrients and their supply. Some of the harmful cardiovascular effects appear to be reversible after cessation of cigarette smoking.

Because of the increasing convergence of epidemiological and physiological findings relating cigarette smoking to coronary heart disease, it is concluded that cigarette smoking can contribute to the development of cardiovascular disease and particularly to death from coronary heart disease.

### *Smoking and Chronic Obstructive Bronchopulmonary Diseases*

Additional physiological and epidemiological evidence confirms the previous findings that cigarette smoking is the most important cause of chronic non-neoplastic bronchopulmonary disease in the United States.

Cigarette smoking can adversely affect pulmonary function and disturb cardiopulmonary physiology. It is suggested that this can lead to cardiopulmonary disease, notably pulmonary hypertension and cor pulmonale in those individuals who have severe chronic obstructive bronchitis.

### *Smoking and Cancer*

Additional evidence substantiates the previous findings that cigarette smoking is the main cause of lung cancer in men. Cigarette smoking is causally related to lung cancer in women but accounts for a smaller proportion of cases than in men. Smoking is a significant factor in the causation of cancer of the larynx and in the development of cancer of the oral cavity. Further epidemiological data strengthen the association of cigarette smoking with cancer of the bladder and cancer of the pancreas.

## Smoking and Overall Mortality

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The 1964 Advisory Committee's Report (3) clearly and emphatically outlined the dangers of cigarette smoking to health. The conclusions of the Committee, as outlined in the 1967 Report (2), were as follows:

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

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

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

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

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

Possible relationships of death rates to other forms of tobacco use were also investigated \* \* \*. The death rates for men smoking less than 5 cigars a day are about the same as for nonsmokers. For men smoking more than 5 cigars daily, death rates are slightly higher. There is some indication that these higher death rates occur primarily

in men who have been smoking more than 30 years and who inhale the smoke to some degree. The death rates for pipe smokers are little if at all higher than for nonsmokers, even for men who smoke 10 or more pipefuls a day and for men who have smoked pipes more than 30 years.

In fact, the Committee's concern was of such an immediate nature that they recommended: "\* \* \* appropriate remedial action."

The 1967 report reviewed the literature of the 3½ years subsequent to the 1964 report and found no evidence to refute the conclusions of the latter.

Additional evidence was given which clarified some of the pathobiomechanisms of the diseases associated with smoking. The findings of the 1964 report were strengthened and some new ones stated. New data on the general mortality and morbidity associated with smoking were presented. The highlights of the 1967 report are given below:

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

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

3. Women who smoke cigarettes show significantly elevated death rates over those who have never smoked regularly. The magnitude of the relationship varies with several measures of dosage. By and large the same overall relationships between smoking and mortality are observed for women as had previously been reported for men, but at a lower level. Not only are the death rates for men who have never smoked regularly higher than those for women who have never smoked regularly, but the effect of smoking as measured either by differences in death rates or by mortality ratios is greater for men than for women. At least part of this can be accounted for by the lower exposure of female cigarette smokers whether measured by number of cigarettes, duration of smoking, or degree of inhalation.

4. Previous findings on the lower death rates among those who have discontinued cigarette smoking are confirmed and strengthened by the additional data reviewed. Kahn's analysis of ex-smokers in the U.S. veterans study—controlling for age at which they began smoking, amount smoked, and current age—reveals a downward trend in risk relative to those who continued to smoke as the duration of time discontinued increases. The British physician study, in which a down-

ward trend is reported in lung cancer death rates for the entire group (smokers, ex-smokers, and those who never smoked, combined) along with a very sharp reduction in cigarette smoking by the physician, is the best available example of a controlled cessation experiment with reduction of risks resulting from reduction of smoking. The findings of this report support the view that epidemiological data showing lower death rates among former smokers than among continuing smokers cannot be dismissed as due to selective bias and that the benefits of giving up smoking have probably been understated.

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

In the 1967 Report the following questions were emphasized:

1. How much mortality and excess disability are associated with smoking?
2. How much of this early mortality and excess disability would not have occurred if people had not taken up cigarette smoking?
3. How much of this early mortality and excess disability could be averted by the cessation or reduction of cigarette smoking?
4. What are the biomechanisms whereby these effects take place and what are the critical factors in these mechanisms?

The problem of how best to measure the relationship between smoking and mortality was presented by three meaningful measures of comparison:

1. **Mortality Ratios:** Obtained by dividing the death rate for a classification of smokers by the death rate of a comparable group of nonsmokers \* \* \* A mortality ratio has been considered to reflect the degree to which a classification variable identifies or may account for variations in death rates. As such, it is a measure of relative risk which indicates the importance of that variable relative to uncontrolled variables—an indicator of *potential biological significance*.

2. **Differences in Mortality Rates:** Obtained by subtracting from the death rate for smokers, the death rate of a comparable group of nonsmokers \* \* \*. This measure reflects the added probability of death in a 1-year period for the smoker over that for the nonsmoker. As such it is a measure of *personal health significance*, a means for the individual to estimate the added risk to which he is exposed.

3. **Excess Deaths:** Obtained by subtracting from the number of deaths occurring in a group of smokers, the number of deaths which would have occurred if that group of smokers had experienced the same mortality rates as a comparable group of nonsmokers. In the example which follows this has been reported as a percentage of all

TABLE 1.—Comparison of mortality rates for smokers and nonsmokers by age and sex: Based on data from U.S. Veterans Study and Hammond Study

Study population, sex, and measure of mortality	35-44 years	45-54 years	55-64 years	65-74 years	75-84 years
<b>U.S. VETERANS: MEN</b>					
Total number of deaths.....	383	366	13,840	17,550	1,932
Death rates per 100,000:					
Never smoked regularly.....	127	264	1,056	2,411	6,214
Current cigarette smokers.....	232	728	1,819	4,032	8,471
Mortality ratio <sup>1</sup> .....	1.83	2.76	1.72	1.67	1.36
Difference in death rates per 100,000 <sup>2</sup> .....	105	464	763	1,621	2,257
Excess deaths as percentage of total <sup>3</sup> .....	33	43	21	17	8
<b>HAMMOND MEN</b>					
Total number of deaths.....	631	5,297	8,427	8,125	3,968
Death rates per 100,000:					
Never smoked regularly.....	210	406	1,202	3,168	7,863
Current cigarette smokers.....	397	925	2,202	4,788	9,674
Mortality ratio <sup>1</sup> .....	1.89	2.28	1.83	1.51	1.23
Difference in death rates per 100,000 <sup>2</sup> .....	187	519	1,000	1,620	1,811
Excess deaths as percentage of total <sup>3</sup> .....	33	38	25	13	4
<b>HAMMOND WOMEN</b>					
Total number of deaths.....	727	2,826	3,915	5,115	4,188
Deaths rates per 100,000:					
Never smoked regularly.....	165	304	698	1,913	5,914
Current cigarette smokers.....	186	384	838	2,229	5,846
Mortality ratio <sup>1</sup> .....	1.13	1.26	1.20	1.17	.99
Difference in death rates per 100,000 <sup>2</sup> .....	21	80	104	316	68
Excess deaths as percentage of total <sup>3</sup> .....	5	9	4	2	-----

<sup>1</sup> Mortality ratios—death rate for current cigarette smokers divided by death rate for those who never smoked regularly.

<sup>2</sup> Differences in death rates—death rate for current cigarette smokers minus death rate for those who never smoked regularly.

<sup>3</sup> Excess deaths among current cigarette smokers (i.e., additional deaths that occurred among current cigarette smokers per year above those which would have occurred if smokers had the same death rates as those who never smoked regularly). This is expressed as a percentage of all deaths occurring in that age-sex group.

SOURCE: The Health Consequences of Smoking (2).

deaths in the appropriate age group \* \* \*. It should be noted that this measure not only depends on the differences in death rates between the smokers and the nonsmokers, but also on the proportion of smokers in the group. Thus, even with a large difference in rates between smokers and nonsmokers, a population with very few smokers would have very few excess deaths. This measure is therefore an indicator of the *public health significance* of the differences found since it measures the number of people affected and therefore the magnitude of the problem for society as a whole.

As seen in table 1, from the 1967 report, the magnitude of the problem is reflected in the statement:

Reviewing both study groups it appears that for men between the ages of 35 and 60 approximately one-third of all deaths that occur are excess deaths in the sense that they would not have occurred as early as they did if cigarette smokers had the same death rates as the non-smoking group. For women, the percentage is much lower, reaching a peak of 9 percent of all deaths in age group 45-54.

Another valuable measure of comparison was recently calculated by Hammond(1), from his study of over 1 million men and women. Life expectancy of men with respect to cigarette smokers and nonsmokers is shown in tables 2 and 3. The life expectancy for a two-pack a day, or more, smoker at age 25 is 8.3 years less than that for the corresponding nonsmoker. Men at age 35 and over, who smoke two or more packs of cigarettes per day, have between 20 and 25 per cent less life expectancy than their corresponding nonsmoking counterparts. Even "light" smokers, those who smoke less than 10 cigarettes per day, have from 2.8 to 4.6 fewer years of life expectancy than corresponding nonsmokers.

TABLE 2.—*Estimated years of life expectancy at various ages for males in the United States, by daily cigarette consumption*

Age	Never smoked regularly	Number of cigarettes smoked per day			
		1-9	10-19	20-39	40 and over
25 years.....	48.6	44.0	43.1	42.4	40.3
30 years.....	43.9	39.3	38.4	37.8	35.8
35 years.....	39.2	34.7	33.8	33.2	31.3
40 years.....	34.5	30.2	29.3	28.7	26.9
45 years.....	30.0	25.9	25.0	24.4	23.0
50 years.....	25.6	21.8	21.0	20.5	19.3
55 years.....	21.4	17.9	17.4	17.0	16.0
60 years.....	17.6	14.5	14.1	13.7	13.2
65 years.....	14.1	11.3	11.2	11.0	10.7

SOURCE: Hammond, E. C. (1).



TABLE 3.—*Loss in life expectancy at various ages for cigarette smokers compared with nonsmokers*

[Loss in years is also expressed as a percent of the total life expectancy of nonsmokers]

Age	Number of cigarettes smoked per day							
	1-9		10-19		20-39		40 and over	
	Years lost	Percent	Years lost	Percent	Years lost	Percent	Years lost	Percent
25 years.....	4.6	9.5	5.5	11.3	6.2	12.8	8.3	17.1
30 years.....	4.6	10.5	5.5	12.5	6.1	13.9	8.1	18.5
35 years.....	4.5	11.5	5.4	13.8	6.0	15.3	7.9	20.2
40 years.....	4.3	12.5	5.2	15.1	5.8	16.8	7.6	22.0
45 years.....	4.1	13.7	5.0	16.7	5.6	18.7	7.0	23.3
50 years.....	3.8	14.8	4.6	18.0	5.1	19.9	6.3	24.6
55 years.....	3.5	16.4	4.0	18.7	4.4	20.6	5.4	25.2
60 years.....	3.1	17.6	3.5	19.9	3.9	22.2	4.4	25.0
65 years.....	2.8	19.9	2.9	20.6	3.1	22.0	3.4	24.1

Source: Hammond, E. C. (1).

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## **PART II**

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### **Technical Reports on the Relationship of Smoking to Specific Disease Categories**

# CHAPTER 1

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## Smoking and Cardiovascular Diseases

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## INTRODUCTION

The primary purpose of the 1968 Supplemental Report is to review the pertinent literature that has become available subsequent to the 1967 Report. Brief mention of the conclusions of the 1964 Report and the highlights of the 1967 Report is made to facilitate an understanding of the significance of the most recent information. The current research findings should be considered in the perspective of the research evidence previously presented in the 1964 (148) and 1967 (146) Reports.

### CONCLUSIONS OF THE 1964 REPORT (148)

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

### HIGHLIGHTS OF THE 1967 REPORT (146)

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

2. Cigarette smoking males have a higher coronary heart disease death rate than nonsmoking males. This death rate may, on the average, be 70 percent greater, and, in some, even 200 percent greater or more in the presence of other known "risk factors" for coronary heart disease. Female cigarette smokers also have a higher coronary heart disease death rate than do nonsmoking females, although not as high as that for males. In general, the death rates from this disease increase with amount smoked. Cessation\* of cigarette smoking is followed by a reduction in the risk of dying from coronary heart disease when compared with the risk incurred by those who continue to smoke.

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

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

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\*Those who have stopped smoking cigarettes have a lower risk of dying from coronary heart disease than those who continue to smoke.

## SMOKING AND CORONARY HEART DISEASE

### CORONARY HEART DISEASE MORTALITY

As in the past two decades, coronary heart disease in the United States continues as the leading cause of death, being responsible in 1967 for 567,710 deaths or 31.0 percent of the total of 1,833,900 deaths.

Since age specific data are not yet available for 1967, table 1 shows the number of deaths due to coronary heart disease and the death rates per 100,000 persons by age for 1966.

TABLE 1.—*Coronary heart disease deaths and death rates per 100,000 population, by age: United States, 1966*

[Disease category 420 in the ICD Manual, 1957]

Age	Number of deaths	Death rates
Total.....	573, 191	292. 7
Under 25 years.....	250	0. 3
25-34 years.....	1, 469	6. 6
35-44 years.....	12, 522	52. 0
45-54 years.....	45, 997	206. 3
55-64 years.....	99, 647	577. 3
65-74 years.....	162, 555	1, 405. 2
75-84 years.....	171, 737	2, 979. 5
85 and over.....	78, 854	7, 015. 5
Not stated.....	160	(X)

X—Not applicable.

SOURCE: Monthly Vital Statistics, National Center for Health Statistics (147).

These data illustrate the dramatic increase in death rates as age advances, with the increase being particularly marked after age 45. The death rates for coronary heart disease for men and women continue to show a conspicuous difference. In 1966 it was 361.6 for males and 226.5 for females per 100,000 population.

While several studies of various aspects of the association between coronary heart disease mortality and cigarette smoking have been reported during the past year, the most significant studies of this association are contained in the 1967 report.

The several new studies of various aspects of the association between coronary heart disease mortality and cigarette smoking follow.

Friedman (46) reported a strong positive correlation between per capita cigarette sales and coronary heart disease death rates by states. The correlation is 0.76 when data only from those states with relatively accurate information of cigarette consumption are analyzed. Related factors such as urbanization or softness of the local water supply do not explain this degree of association.

Other studies deal with the excess deaths associated with smoking. Strobel, et al. (140) reported that among 3,479 Swiss physicians, over 50 percent of the excess deaths occurring over a 9-year period among smokers was due to coronary heart disease.

In contrast to the study above and data from the United States in which approximately one-half of the excess deaths associated with smoking are attributed to cardiovascular causes (148), preliminary data from Hirayama (65) show that the excess deaths in Japan associated with smoking were primarily explained by cancer of various sites. Only 12 percent of the excess deaths were associated with cardiovascular causes. This prospective study of 265,118 adults over the age of 40 encompassed a followup period of 15 months. Additional follow-up by Hirayama should yield useful data with respect to smoking and excess mortality from cardiovascular diseases in this Japanese population group, particularly with regard to the younger adults in the study.

Hyams, et al. (67), on the other hand, speculate that the apparent increase in the occurrence of coronary heart disease among Japanese males, especially under the age of fifty, may be due to a trend toward Westernization in both diet and smoking habits among younger Japanese men.

Hammond (54), in his prospective study of over 1 million men and women, showed a positive relationship between the duration of the smoking habit and coronary heart disease mortality. In the Framingham Heart Study (71), no association was found between the duration of the smoking habit and the incidence of mortality from heart attacks among men who were "heavy smokers" (more than one package of cigarettes per day).

These discrepancies between the relationship of smoking to the incidence of total coronary heart disease and mortality from acute coronary heart disease may be accounted for, in part, by the differences in population groups studied and by the possibility that duration of smoking may have a greater association with the fatal forms of coronary heart disease.

Kannel, et al. (70), in more recent data from the Framingham study, indicate that the fatal and more severe forms of coronary disease are more strongly associated with cigarette smoking than the less severe forms (figure 1).

#### Coronary Heart Disease Morbidity \*

Much of the morbidity data reported during this past year resulted from retrospective studies of patients or cross-sectional studies (106, 107, 127, 134, 151). In these studies the findings revealed that there

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\* Also may include mortality data in this presentation.

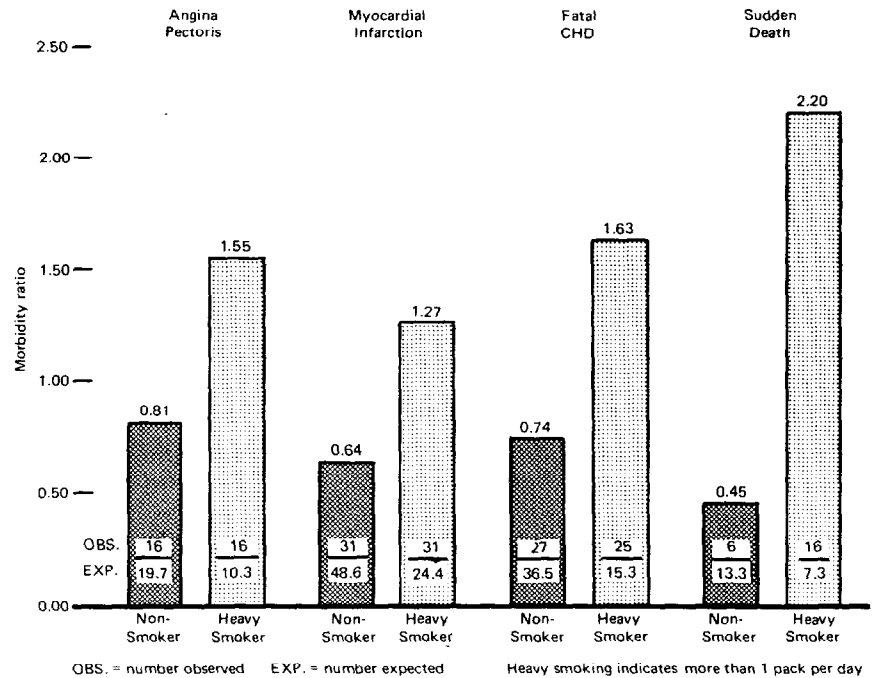


FIGURE 1—Morbidity ratios for specified manifestations of coronary heart disease, among men aged 30–59 years at entry into Framingham Heart Study, classified by smoking habit: 12 years' experience.

SOURCE: Kannel, et al. (70).

were relatively more smokers among the groups with coronary heart disease, than among the comparison, or control groups.

In a retrospective study of myocardial infarction patients in Japan, Hyams, et al. (67) reported similar findings, particularly among the men under age 50. Differences measured by an exposure index combining intensity and duration of smoking showed the same trend, though the data were not statistically significant.

Dorken (30, 31) reported on two retrospective studies in Hamburg, Germany: one, a study of female patients; the other, a study of male patients. He concluded that there is a strong association between smoking and myocardial infarction in both males and females under the age of 45.

In Dublin, Mulcahy, et al. (106, 108, 109) studied groups of male and female coronary heart disease patients under age 60. He found that a much greater portion of the patients, in comparison with a sample of the general population, smoked cigarettes. Also, the intensity (amount multiplied by duration) of smoking was as much as 2½ times greater among the male patients and 3 times greater among the



female coronary heart disease patients as contrasted with the males and females in the general population.

In a study of 675 aviators, smoking histories taken in 1963 did not show a positive association in the prevalence of coronary heart disease with either amount, duration, or intensity of smoking. These findings are based on 38 cases (5.7 percent) of coronary heart disease of all forms among a very select population and are therefore subject to large sampling variations (96). Moreover, since smokers may have an excessive mortality during an acute myocardial infarction, as mentioned before, prevalence rates are not as good a measure of the association between smoking and coronary heart disease as are incidence rates.

Epstein (39), although finding no prevalence differences between smokers and nonsmokers in his Tecumseh Study, found an increased incidence in cigarette smokers of both fatal and nonfatal coronary heart disease.

In a short prospective study of 14,000 Norwegian men (12,000 with smoking histories), Natvig (113) did find an increased risk of incidence of first myocardial infarction or angina pectoris among those men 50-59 years of age who smoked.

Since the 1967 Report, the continuing prospective epidemiologic studies have somewhat clarified the differential relationship between smoking and each of the manifestation categories of coronary heart disease: angina, nonfatal myocardial infarction, fatal myocardial infarction and sudden death.

Data from the Framingham Heart Study (69) revealed that "heavy" cigarette smoking, more than 20 cigarettes per day, is positively associated with uncomplicated angina in males but not in females (figure 2).

Similar findings were reported by Weinblatt (155) in a study of male subjects in the Health Insurance Plan with the associations more pronounced among those men who smoked two or more packages of cigarettes per day. As can be seen, in table 2, the arithmetic differences in rates between smokers and nonsmokers are greater for myocardial infarction than for angina; however, the risk ratios are similar.

In a retrospective study, Heyden-Stucki et al. (61) found no association of smoking with angina or other chest complaints.

The inconsistencies in data on the association between smoking and the development of angina may be due in part to differences in methods used to diagnose and classify angina and to record smoking habits in these epidemiologic studies. Further standardization in this area may help to determine more accurately the relationship of smoking to angina.

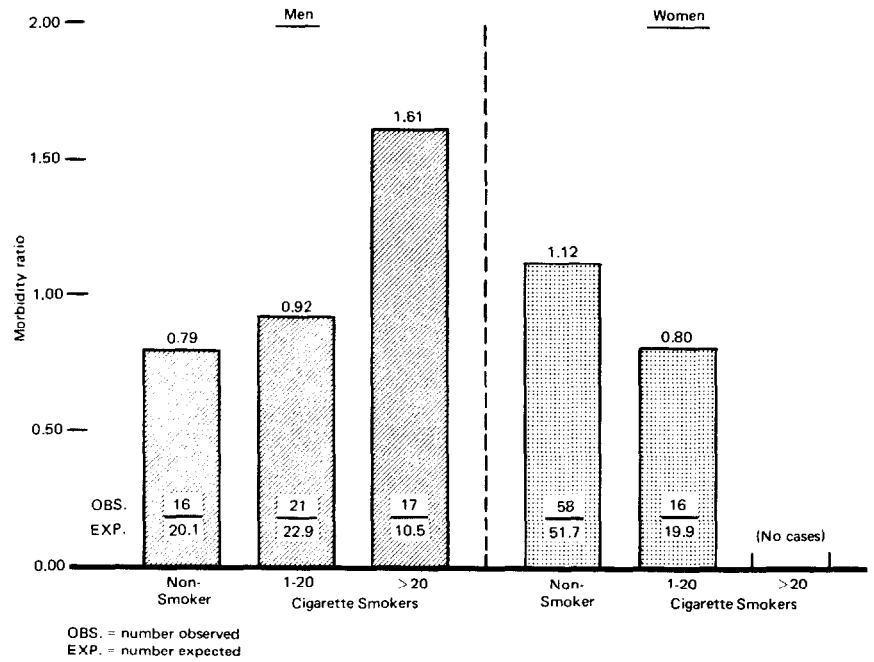


FIGURE 2—Angina pectoris morbidity ratios among persons aged 30-59 years at entry into Framingham Heart Study, classified by sex and number of cigarettes smoked: 12 years' experience.

SOURCE: Kannel, et al. (69).

TABLE 2.—Age-adjusted incidence rates per 1,000 males aged 35-64, and morbidity ratios, for specified manifestations of coronary heart disease, by smoking category: Health Insurance Plan Study

[3 year observation data]

Smoking category	Myocardial infarction		Angina	
	Incidence rate	Morbidity ratio	Incidence rate	Morbidity ratio
Current nonsmokers.....	3.27	1.0	1.37	1.0
Current cigarette smokers.....	7.01	2.1	2.62	1.9
Less than 2 packs.....	5.05	1.5	2.08	1.5
2 or more packs.....	20.80	6.4	6.64	4.8

Source: Weinblatt, E. (155).

In the Western Collaborative Study, Rosenman et al. reported higher rates of silent myocardial infarctions in younger men, and higher rates of recurrent myocardial infarctions at all ages among those who smoked more than 25 cigarettes per day (123, 124).

Friedemann, et al. (44) reported reinfarctions occurred more frequently among smokers than nonsmokers.

Dorken (29) found in a series of 330 men of all ages, in Hamburg, who survived at least 3 and up to 6 years after their first myocardial infarction, that 172 (52 percent) had stopped smoking completely after the first infarction. In contrast, of 85 subjects who had died from a second myocardial infarction or sudden coronary death after leaving the hospital, only 28 (32.9 percent) had given up smoking completely ( $P < 0.001$ ).

#### RELATIONSHIPS OF CIGARETTE SMOKING TO OTHER RISK FACTORS

The ongoing prospective and other epidemiologic studies have yielded findings which permit analysis of the interrelationships among cigarette smoking and other factors considered to increase the risk of coronary heart disease.

##### *Age*

Generally, the findings show that the incidence rate of coronary heart disease increases with age, both among smokers and nonsmokers. The morbidity ratio of coronary heart disease in smokers versus nonsmokers decreases with age though the absolute number of excess deaths among smokers increases with age.

##### *High Blood Pressure*

Recent reports on the relationship between smoking and blood pressure appear to support the findings in the 1967 report:

Although the inhalation of cigarette smoke is frequently accompanied by acute transient elevations in blood pressure, habitual smokers tend to have lower blood pressures than do nonsmokers. But, given the presence of high blood pressure in an individual, smoking acts as an additional risk factor for the development of coronary heart disease.

Heyden-Stucki et al. (61) report that among 500 workers in Switzerland, smokers, particularly heavy smokers, have lower blood pressure as a group than do nonsmokers. Smokers also were found to have normal or subnormal weights in contrast to nonsmokers who had a greater mean weight; thus, confounding the relationship between smoking and blood pressure level. Tibblin (144) in a cohort study of Scandinavian men born in 1913, found a lower mean blood pressure among smokers than among nonsmokers. As the population was classified according to levels of blood pressure, a step-wise decrease in the prevalence of smoking was noted as the level of blood pressure in-

TABLE 3.—Mean age and mean systolic and diastolic blood pressure, by smoking category: Los Angeles Heart Study, 1962

Current cigarette smoking status			Blood pressure (mm. of Hg.)	
	Number of subjects	Years of age	Systolic	Diastolic
Smokers.....	407	54	133. 6	82. 5
Nonsmokers.....	728	57	137. 0	83. 9

SOURCE: Clark, V. A. (23).

creased. A similar trend for both systolic and diastolic pressures was also reported by Clark, et al. (23) as shown in table 3.

In the study of 675 aviators (96) smoking intensity, although not found to be associated significantly with systolic or diastolic blood pressures, was positively associated with pulse pressure. Reid, et al. (122) in a comparative study of workers in Great Britain and the United States noted lower diastolic blood pressures among smokers than among nonsmokers in both groups; adjustment for weight variations reduced this difference appreciably.

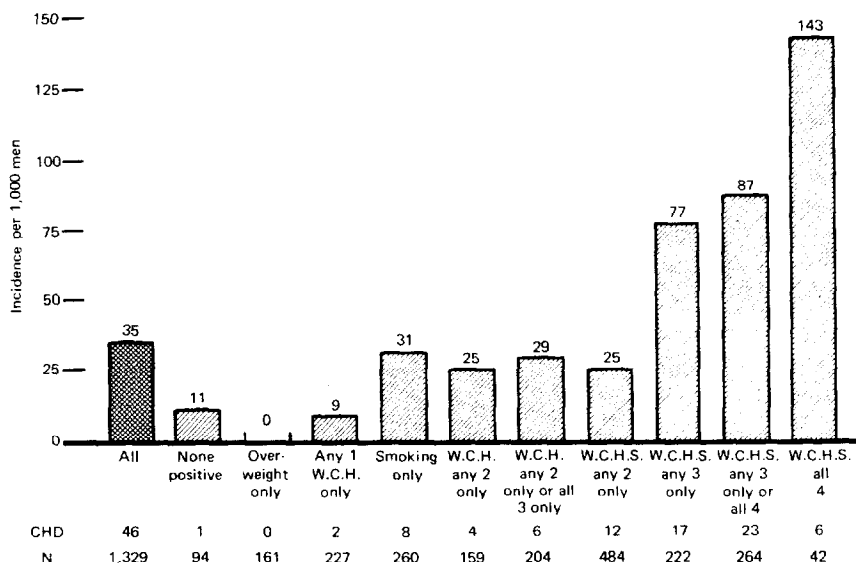
Mulcahy (107), in a retrospective study of 100 women coronary heart disease patients under 60 years of age, reported that 50 to 60 percent had diastolic hypertension (>90 mm. Hg.). Hypertension and cigarette smoking, together or separately, were present in over 80 percent of these patients.

In the major prospective studies, when both smoking and hypertension were present, an interactive increase in the risk of developing coronary heart disease was noted. When to these two risk factors elevated cholesterol levels were added, the risk of developing coronary heart disease was further increased (figures 3 and 4).

#### *High Serum Cholesterol and Related Diet*

Certain of the retrospective and cross-sectional studies (62, 151) have, in general, demonstrated higher cholesterol levels in smokers than in nonsmokers. Pincherle, et al. (119) and Lane, et al. (96) report similar findings. A study by Heyden-Stucki (61) of 500 Swiss workers found a similar trend but the differences between smokers and nonsmokers with respect to cholesterol levels and other lipids were not statistically significant.

A recent report (36) describes some of the variability of interrelationships among smoking, blood pressure and cholesterol levels in different population groups throughout the world. It concludes that though nonsmokers tend to be heavier and have higher blood pressure levels than cigarette smokers, heavy smokers tend to be in the top



Relationship between status with respect to four coronary risk factors (hypercholesterolemia, hypertension, overweight, and cigarette smoking) as evaluated on original examination and incidence of clinical coronary heart disease in men originally age 40-59, free of definite CHD, and followed subsequently without systematic intervention, Peoples Gas Light and Coke Company study, 1958-1962. W is overweight, ie, a ratio of observed weight to desirable weight of 1.15 or greater; C is hypercholesterolemia, ie, serum cholesterol level of 250 mg/100 ml or greater; H is hypertension, ie, a diastolic blood pressure of 90 mm. Hg or greater; S is smoking of ten or more cigarettes per day.<sup>1</sup>

FIGURE 3—Incidence of coronary heart disease among men aged 40-59 years at entry into Peoples Gas Light and Coke Company Study, classified as to presence of specified risk factors: 1958-1962.

SOURCE: Stamler, et al. (138).

deciles for blood pressure and relative weight. Cholesterol-smoking relationships described in these studies do not show a consistent pattern.

In a controlled dietary intervention study of postinfarction patients Leren (97) found that smoking habits did not influence the serum cholesterol level or the coronary heart disease relapse rate in the control group. Among the study group of dieters there was a suggestion, although not statistically significant at the 0.05 level, that smokers had a higher coronary heart disease relapse rate than nonsmokers.

#### Physical Inactivity

The independent and combined effects of cigarette smoking and physical activity, as described in the 1967 report, continue to be demonstrated as more data are accumulated. The apparent protective effect of physical activity appears to be more pronounced with regard to myocardial infarction than angina [table 4, (155)]. Differences in methods of assessment of history of physical activity in case versus

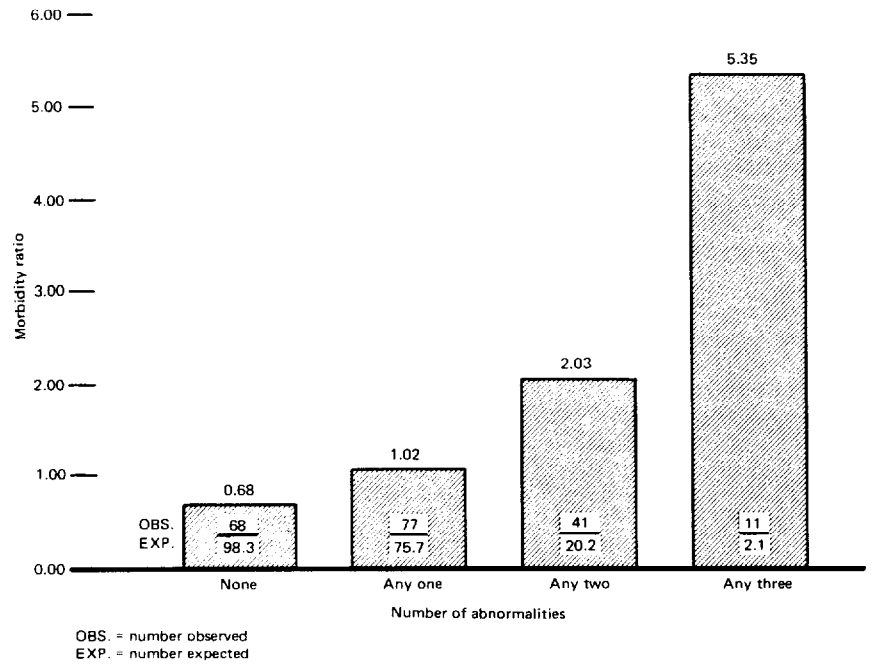


FIGURE 4—Myocardial infarction morbidity ratios among men aged 30-59 years at entry into Framingham Heart Study, classified according to presence of selected risk factors: 12 years experience (Risk factors are: cholesterol level over 250 mg/100 ml, systolic blood pressure over 160 mm. Hg., smoking over 1 pack of cigarettes per day).

SOURCE: Kannel, et al. (70).

control groups may account for some differences in the incidence rates noted.

Blackburn, et al. (10) found no relationship of smoking to the prevalence of postexercise ECG changes in a study of 10,260 men age 40 to 59 years. However, there were only 519 (5.1 percent) subjects with a "positive" ECG response.

#### *Sociological, Psychological and Personality Variables*

Two studies (45, 64) demonstrated an inverse relationship between the frequency of coronary heart disease and the educational level of the subjects. In the Bell Telephone System (64), those men without a college education had higher coronary heart disease rates than those with a college education. Also, those not attending college tended to smoke more.

In a study of factors related to coronary heart disease among Cleveland attorneys (45), the quality of the law schools attended by the sub-

TABLE 4.—Annual age-adjusted incidence rates of specified manifestations of coronary heart disease per 1,000 males aged 35–64 and corresponding morbidity ratios, by smoking habits and physical activity class: Health Insurance Plan Study

[3 year observation data]

Smoking status and physical activity class	Myocardial infarction		Angina	
	Incidence rate	Morbidity ratio	Incidence rate	Morbidity ratio
All current nonsmokers.....	3.27	1.0	1.37	1.0
Not cigarette smokers:				
Least active.....	6.33	1.9	2.14	1.6
Intermediate.....	3.07	0.9	1.67	1.2
Most active.....	3.01	0.9	1.32	1.0
All current cigarette smokers:				
Least active.....	10.89	3.3	2.31	1.7
Intermediate.....	5.80	1.8	2.83	2.1
Most active.....	5.77	1.8	2.74	2.0
Less than 2 packs:				
Least active.....	7.61	2.3	2.05	1.5
Intermediate.....	4.71	1.4	2.37	1.7
Most active.....	3.85	1.2	1.95	1.4
2 or more packs:				
Least active.....	39.09	12.0	4.97	3.6
Intermediate.....	11.27	3.5	5.09	3.7
Most active.....	24.09	7.4	12.20	8.9

Source: Weinblatt, E. (165).

ject were ranked independently by a law school professor. Lawyers attending schools in the "highest law school quality group" had lower rates of coronary heart disease than those attending schools in the "lower law school quality group." Also, those in the latter group had started smoking at an earlier age. Since additional differences were noted for other risk factors, smoking alone may not be responsible for the total differences in these rates. In both studies, it was hypothesized that with respect to susceptibility to development of coronary heart disease, behavior patterns and attitudes established prior to professional training and prior to stresses resulting from job mobility and job tension, were more significant than the later stresses which resulted from their present jobs.

Recent data from the Western Collaborative Group Study (125) appear to show that among men 39–49 years of age, cigarette smoking was associated with several coronary heart disease risk factors (table 5). Though these findings may be statistically significant, the differences between smokers and nonsmokers were small.

TABLE 5.—Age-adjusted means for selected coronary heart disease risk factors and personal characteristics, by smoking category: Western Collaborative Group Study, males 39-49 years of age

[4½ years average observation data]

Variable	Smoking category		Percent difference
	Never smoked	Smoked 26 cigarettes or more per day	
Serum cholesterol.....	217. 2	231. 8	+6. 7
Beta/alpha ratio.....	1. 9	2. 1	+10. 5
Lipalbumin.....	21. 1	19. 4	-8. 1
Systolic blood pressure.....	126. 3	129. 9	+2. 9
Diastolic blood pressure.....	82. 0	81. 3	-0. 9
Ponderal index.....	12. 6	12. 7	+0. 8
Physical activity on job.....	1. 95	1. 95	0
Amount of exercise.....	2. 18	2. 05	-6. 0
Income.....	2. 75	2. 75	0

Source: Rosenman, R. H. (125).

TABLE 6.—Percent distribution by behavior type of smokers and non-smokers: Western Collaborative Group Study, males 39-49 years of age

[4½ years average observation data]

Behavior type	Total	Smoking category					
		Never smoked	Former smokers	Current pipe or cigar only	1-15 cigarettes per day	16-25 cigarettes per day	26 cigarettes or more per day
Total.....	100. 0	100. 0	100. 0	100. 0	100. 0	100. 0	100. 0
Type A.....	47. 5	41. 3	45. 0	48. 3	44. 8	48. 9	56. 7
Type B.....	52. 5	58. 7	55. 0	51. 7	55. 2	51. 1	43. 3

Test of difference of distributions:  $X^2=24.70$ ;  $df=3$ ;  $p=.001$ .

SOURCE: Rosenman, R. H. (125).

Behavioral pattern type A is characterized by an enhanced competitiveness, drive, aggressiveness and hostility, and an excessive sense of time urgency as contrasted to type B. There was a difference in the distribution of personality types A and B among smokers and nonsmokers (table 6).

The foregoing data refer to concurrent observations gathered in 1960-1961 on 3,182 men who were then free of manifestations of coronary heart disease. A follow-up of this population during the



next 4½ years disclosed that cigarette smokers experienced substantially higher rates of coronary heart disease than those who had never smoked. This finding is based on data for men 39–49 years of age, which have been adjusted for the confounding influences of related risk factors, such as age, cholesterol, etc. (table 7).

TABLE 7.—*Incidence of new coronary heart disease by smoking category: Western Collaborative Group Study, males 39–49 years of age*

[4½ years average observation data]

Smoking category	Number of men	Rate per 10,000 population	
		Adjusted for concomitant variables	Not adjusted
Never smoked.....	540	36	29
Former cigarette smokers.....	241	67	92
Pipe and cigar only.....	406	27	16
1–15 cigarettes.....	212	51	52
16–25 cigarettes.....	436	89	92
26 cigarettes and over.....	425	98	104

SOURCE: Rosenman, R. H. (125).

The coronary heart disease rate for those men smoking 26 or more cigarettes a day is seen to be about three times greater than for those who never smoked. The rate for former smokers is still rather high, even after adjustment for concomitant variables. The largest impact of the adjustment procedure is noted among this group, and suggests that those who quit may have done so because they were already a relatively high-risk group for reasons other than smoking. The relatively low rate among men smoking only pipes and cigars is noted in this as in other prospective studies.

The nature of the association of smoking and coronary heart disease incidence among type A and type B personality groups is not easy to characterize or interpret. Among the type A group, the pipe and cigar smokers and the light cigarette smokers had the lowest rates of incidence of new coronary heart disease, while the highest rates were found among those smoking 26 or more cigarettes a day. For the type B group, the lowest rates occurred among those who had never smoked, and the highest among the light cigarette smokers. The age-adjusted rates of new incidence of coronary heart disease per 10,000 men 39–49 years of age are shown in table 8.

Additional data to permit concomitant analysis of these variables and those in table 7 are needed.

TABLE 8.—*Incidence of new coronary heart disease by smoking category and behavior type: Western Collaborative Group Study, males 39-49 years of age*

[4½ years average observation data]

Smoking category	Rate per 10,000 population	
	Behavior type A	Behavior type B
Total.....	91	33
Never smoked.....	53	13
Former smokers.....	107	36
Pipe and cigars only.....	18	36
Cigarettes:		
1-15.....	18	60
16-25.....	135	33
26 and over.....	149	51

SOURCE: Rosenman, R. H. (125).

Lane, et al. (96) found significant relationships of smoking intensity and duration with personality factors—impulsiveness, emotional instability and belligerence scales.

Thomas (143) after reviewing various studies of psychological variables related to coronary heart disease, concludes that smoking may have different effects on different personality types and at different anxiety levels.

#### *Multiple Risk Factors*

The acceptance of a multiple factor causation hypothesis for coronary heart disease emphasizes the need for more sophisticated statistical analyses of appropriate data. Our understanding of the relative importance of various risk factors from the limited number of such special analyses has not been altered significantly from that obtained by more conventional statistical analyses (38).

Clarification of the apparent independence of several of the major risk factors has resulted.

Truett, et al. (145) emphasize that the major risk factors are noted to have a different order of importance by age and sex. Cigarette smoking is particularly important among younger males as noted in table 9.

#### *Genetic and Constitutional Studies*

Baer (5) found that heavy smokers among college males were taller than light smokers and nonsmokers. Lane, et al. (96) also found significant associations between body size measurements, including ponderal index (though not with height or weight individually), and amount of smoking in the study of over 675 aviators.

TABLE 9.—*Linear discriminant function coefficients (in standard units) for various risk factors in coronary heart disease, by sex and age: 12 Year Framingham Study*

Risk factors	Men				Women		
	Combined ages	30-39 years	40-49 years	50-62 years	Combined ages	30-49 years	50-62 years
Age.....	0. 5934	0. 2394	0. 3334	0. 2370	0. 6259	0. 7325	0. 2600
Cholesterol.....	0. 4444	0. 9613	0. 3207	0. 3790	0. 2844	0. 7322	0. 1207
Systolic blood pressure.....	0. 3334	0. 3427	0. 1669	0. 3809	0. 5556	0. 1947	0. 4776
Relative weight.....	0. 1890	0. 1941	0. 3619	0. 1036	0. 0975	0. 0751	0. 1481
Hemoglobin.....	-0. 1050	0. 0313	-0. 0134	-0. 2206	0. 0392	-0. 0304	0. 0734
Cigarettes smoked.....	0. 4192	0. 6823	0. 5084	0. 3004	0. 0625	-0. 0731	0. 1262
ECG abnormality.....	0. 2626	0. 2685	0. 2556	0. 2197	0. 3048	0. 2234	0. 2526

SOURCE: Truett, J. (145.)

Cederlof (18) has emphasized the value of studies of twins for investigating aspects of coronary heart disease and presents certain suggested modifications in methodology. The 1967 Report (146) discussed the studies by Cederlof on Swedish twin pairs (19, 20). His data on American twin pairs was recently presented and showed results similar to those of the Swedish twins (18).

The problems with interpretation of these studies are several. The small numbers of cases and the combining of data for both sexes in various subcategories make rates and ratios subject to significant chance variations. In addition, use of a questionnaire for angina, with only modest levels of reliability and validity requires a larger study population before definitive conclusions can be made. The lack of information on the distribution of risk factors other than smoking in subsamples of discordant twin pairs and the total group of twin pairs makes the comparison of ratios for prevalence of symptoms difficult to evaluate. The inclusion in the "smoking" group of those who had stopped smoking up to 3 years previous to the study, would also tend to diminish the differences between smokers and nonsmokers. Definitions of discordant smoking habits must conform to those differences identified as significant in the large-scale population studies.

The fact that discordance for smoking does occur among monozygotic twins certainly indicates that the smoking habit cannot be determined by genetic factors alone. Twin studies with further sophistication of design, larger number of cases, better definitions of disease, and more significant identification of discordant exposures have the potential of contributing substantially to our understanding of the interactive factors in coronary heart disease.

In an article reviewing some of the epidemiological evidence in the 3½ years subsequent to the 1964 report, Seltzer (129) concluded that there was no substantial evidence to indicate a further association of cigarette smoking with coronary heart disease beyond that stated in the 1964 report.

Seltzer alluded to what he called "inconsistencies" in the recent literature relating to duration, amount, age, inhalation and mode of tobacco smoking with coronary heart disease.

The addition of many more person years of experience, from the new and continuing studies, provides data since the 1964 Report that can be analyzed age-specifically. When this is done most of these "inconsistencies" disappear.

Seltzer's conclusion is contrary to that of most epidemiologists who are familiar with the current research. Furthermore, he has not considered the important relevance of the experimental, pathological, and clinical data that have been reported since 1964 concerning cigarette smoking and cardiovascular diseases.

#### INFLUENCE OF SMOKING AND NICOTINE ON BLOOD LIPIDS

##### *Epidemiological Studies*

The results of epidemiological studies on the relationship of smoking to serum lipid levels have not been consistent. Several studies reported no significant difference in serum cholesterol (36, 40, 61, 150) and triglyceride levels (40, 61) between smokers and nonsmokers. In their study of twins, Blomstrand, et al. (11) state that prolonged smoking had an insignificant effect on all serum lipid levels in their monozygotic twins and only elevated phospholipids in their dizygotic group. However, they quote a personal communication from Carlson, et al. who found elevated triglyceride levels in smokers in a prospective study of 6,000 persons.

In a very comprehensive study of 657 former naval aviation cadets over a period of 23 years, Harlan, et al. (56) investigated the relationship of various constitutional and environmental factors to serum lipid and lipoprotein levels. They found that serum Sf 0-12 (beta) lipoproteins and cholesterol levels were related to cigarette smoking and that the duration of smoking also had a significant correlation. The authors felt that the relationship of smoking to these lipids was presumably direct, because cigarette smoking did not correlate with other factors related to lipids.

##### *Experimental Studies—Animal*

Studies in dogs of the immediate effects of tobacco smoke inhalation and nicotine administration showed an increase in serum triglycerides but not cholesterol, in addition to a rise in free fatty acids (76). There

were no differences in cigarette, cigar or pipe smoke effects when the depth of inhalation was kept constant. Chronic administration of nicotine in dogs resulted in a 50 percent rise in serum cholesterol levels but did not affect triglycerides (82). Kershbaum, et al. (83) have also shown that pronethalol (a beta-receptor blocker) inhibits the serum-free fatty acid and triglyceride rise induced by nicotine in dogs.

In studies of the lipid and atherogenic effects of chronic nicotine administration in cholesterol-fed rabbits, one report found no effect in serum lipid levels but a significantly higher incidence of aortic fibrosis (51). Other investigators found that nicotine increased the amount of cholesterol in the blood and the intensity of lesions in the aorta (28). In cholesterol-fed rabbits administered vitamin D, Hass, et al. (59) found that nicotine induced severe calcific athero-arteriosclerosis and occlusive thromboarteritis, especially conspicuous in cardiac, smooth and skeletal muscle.

Astrup (2) has shown that in rabbits on a high cholesterol diet, chronic carbon monoxide exposure had a marked atherogenic effect.

Gudbjarnason (52) has shown that chronic nicotine administration in dogs leads to a diminution in the rate of cholesterol turnover.

#### *Studies in Humans*

It has previously been reported (78) that cigarette smoking mobilizes free fatty acids, resulting in increased plasma concentrations. It was also found that this effect of smoking was the result of increased sympathetic and adrenal activity initiated by the absorbed nicotine (84), the latter having no direct lipolytic action in adipose tissue (85). This response to smoking has now been confirmed by other investigators (41, 90, 110).

Studies in man, on the immediate effect of cigarette smoking, have shown no effect on serum concentrations of lipoproteins and lipoprotein lipids (cholesterol, phospholipids, triglycerides) (78, 92, 115). In a recent study, however, an increase in serum beta-lipoproteins was observed 10 minutes after smoking (72).

In a study of the comparative effects of cigarette, cigar and pipe smoking on free fatty acid mobilization and catecholamine excretion, cigarette smoking was found to have a much greater effect (81). Less nicotine absorption in cigar and pipe smoking, due to the absence of inhaling, was considered to be the explanation for the milder biochemical effects with these two forms of smoking (80). Kershbaum, et al. also compared the effects of various types of cigarettes on these parameters (79). They found no difference in free fatty acid and catecholamine response or nicotine absorption with several brands of filter and non-filter cigarettes. Cigarettes containing shredded lettuce leaf had no effect.

In other lipid studies it was observed that smoking might increase the tendency of human blood serum to crystallize cholesterol (87).

Kershbaum has also shown that cigarette smoking increases the blood steroid levels in humans (86).

#### STUDIES ON THROMBUS FORMATION

The 1967 Report reviewed the effects of smoking on *in vitro* thrombus formation, varying platelet characteristics and other serum factors associated with blood coagulation. It is not in the scope of this report to go into a detailed analysis of blood coagulation and/or thrombosis. However, the role of smoking and blood lipids on thrombogenesis will be briefly discussed, as they relate to thrombosis and cardiovascular disease.

##### *Catecholamines*

The role of catecholamines (especially epinephrine) in thrombogenesis must be stressed (111). The nicotine-induced catecholamine release, which plays a major role in cardiovascular dynamics might also be the mediating factor in the relation between cigarette smoking and thrombosis. Ardlie (1) has shown that catecholamines enhance ATP or ADP induced platelet aggregation. ADP and noradrenaline in low concentration (up to 0.05  $\mu\text{g./ml.}$ ) were found to increase platelet mobility (55). The reverse was true in higher concentration. Rowsell (128) has shown increases in both thrombus formation in an extracorporeal system and clotting time in silicon-coated tubes with moderate doses of epinephrine. Large doses gave values closer to the control state. Besterman (8) has shown a diurnal variation in "platelet" stickiness which might be associated with diurnal variations in catecholamine release. Glynn (48) found no difference in platelet aggregation between smokers and nonsmokers.

Shimamoto (133) proposes that epinephrine has a primary effect on the arterial wall causing the release of a thromboplastin-like substance which then leads to increased platelet aggregation. An autopsy study in humans by Auerbach (3) showed increased fibrous thickening in the walls of arterioles and small arteries of 5 organs, in smokers as compared to nonsmokers. This effect might be secondary to platelet changes which then caused damage to the arterial wall. As discussed earlier in the study by Hass (59), in which rabbits on a high cholesterol and vitamin D diet were given nicotine, at the site of the occurrence of thrombus there was usually an inflammation of the arterial wall.

##### *Blood Lipids*

Conner, et al. (26) and Warner, et al. (153) have described various experiments in dogs and rabbits, in which infusion of long-chain saturated free fatty acids caused extensive thrombosis and death. *In*

*vitro* coagulation and platelet aggregation were also increased. Long-chain unsaturated free fatty acids, however, did not have these effects although microscopic platelet aggregation was observed (66). *In vitro* studies have shown that linoleic and linolenic acids might have a protective effect against platelet aggregation induced by long-chain saturated fatty acids (73, 101).

The rise in plasma-free fatty acids which follows cigarette smoking was associated with increased platelet adhesiveness (110). The long-chain fatty acid-induced platelet aggregation was suggested to be due to ADP release from platelets (58). Harrison (57) suggests that *in vitro* platelet adhesiveness tests are influenced by ADP release from damaged red cells and that the platelet change might really be a reflection of red cell abnormalities.

Bray (14) found that coronary heart disease patients have an exaggerated platelet adhesiveness in response to ADP or ATP.

Several studies have shown disturbances in lipid and carbohydrate metabolism in coronary heart disease patients (24, 95, 136).

Kurien (95) postulates that the increases in free fatty acid levels immediately after either an acute myocardial infarction or cerebrovascular accident result from tissue anoxia with a secondary catecholamine release, which then leads to the increases in free fatty acids. Malhrotra (103) studied two population groups in India. There was no difference in the cholesterol, triglyceride, and free or esterified fatty acid levels between the two groups. However, the incidence of coronary heart disease was much higher in the population whose diet and fat absorption predispose to an abundance of long-chain fatty acids.

A majority of coronary heart disease patients have an abnormal glucose tolerance test. In most of these patients there is a greater decrease in free fatty acids in response to glucose and a slower return to normal values (24, 136).

Soloff and Schwartz (136) have determined two subgroups of these patients: one "A", in which the free fatty acid response to glucose resembled a normal curve except for an exaggerated rise after 5 hours; another "B", in which the free fatty acid response to glucose resembled that of diabetics, there being a slower decrease and a subnormal return of free fatty acid levels after 5 hours. The significant effect, however, is that type "B" patients had a relative hyporesponse of stearic acid (long-chain saturated) decline with a relatively decreased rise in linoleic acid (long-chain unsaturated) after 5 hours.

These findings may be related to the effect of saturated and unsaturated fatty acids on blood coagulation and suggest further research to delineate the specific fatty acids elicited after smoking and in coronary heart disease patients.

## CARDIOVASCULAR RESPONSE TO SMOKING AND/OR NICOTINE

This section should be read in conjunction with the findings reviewed in the 1967 report.

### *Experimental Studies*

Nadeau, et al. (112) cannulated the sinus node artery in anesthetized dogs and noted chronotropic changes in response to doses of nicotine ranging from 1.0 to 100  $\mu\text{g./ml}$ . Intranodal atropine abolished bradycardia and intranodal propranolol or hexamethonium abolished tachycardia. Nicotine inhibited the effects of cervical vagus nerve stimulation without modifying the response to intranodally injected acetylcholine. Nicotine did not inhibit the effect of stellate ganglion stimulation. These results illustrate the varying effects of nicotine under experimental conditions on the complicated neural and humoral mechanisms affecting heart rate and rhythm.

Sleight (135) and Bergel, et al. (7) have demonstrated cardiovascular depressor reflexes in dogs elicited by nicotine stimulation of the surface of the left ventricle. Studies have been undertaken in dogs to determine the effect of beta sympathetic receptor blockade by propranolol on the cardiac actions of nicotine. Westfall (158), Edmundowicz (32), Papacostas, et al. (116), Shanks (131) and Puri (120) have noted that propranolol can prevent the usual positive inotropic effects of nicotine or norepinephrine stimulation on the myocardium as well as the indirect beta dilator effects on peripheral vessels. This results proportionately in a greater increase in left ventricular afterload accompanied by a reciprocal decline of the velocity of myocardial fiber shortening (120). It was also noted that resulting unopposed alpha receptor activation by nicotine could lead to increased total peripheral resistance with impaired stroke volume and cardiac output. This is further evidence that catecholamines, the release of which is induced by smoking, intermediate the cardiovascular response to nicotine.

The effect of nicotine in single and repeated administrations was studied on the terminal vascular bed of the heart by Corsini, et al. (27). Results indicated that in dogs with intact coronary circulations, the single intravenous infusion of nicotine (150  $\mu\text{g./kg. body weight/minute}$ ) increased both the left ventricular capillary blood flow as well as the terminal vascular capacity; the chronic intramuscular administration (0.5 mg. kg. body weight given 5 times/day for 2 months), however, had no such effect. In contrast, in dogs with constriction of the coronary arteries, nicotine administration in either (single or repetitive doses) form resulted in a fall of capillary blood flow but an increase in the terminal vascular capacity. Capillary blood flow as measured in these studies represents a nutrient inflow to the myocardium. Nicotine administration resulted in an increase in both



the velocity of myocardial shortening as well as the force of contraction, and these effects of nicotine are identical to those of norepinephrine. In addition, there was also an increase in the rate of left ventricular pressure rise ( $dp/dt$ ) and a decline in left ventricular end-diastolic pressure (121).

Coleman, et al. (25) studied isolated cat papillary muscles to determine the mechanism of the norepinephrine-induced stimulation of myocardial oxygen consumption. They found that norepinephrine does not increase the myocardial tissue oxygen demand unless contractility is increased, other factors being held constant. Norepinephrine is known to increase myocardial contractility.

Further studies (49, 142) on anesthetized open-chest dogs to determine the relative influences of changes in either the contractile state or in tension development on myocardial tissue oxygen consumption, indicate that both are significant factors. Basal oxygen requirements, activation energy, and the cost of contractile element shortening against a load appear to influence myocardial tissue oxygen consumption to a lesser degree.

Chidsey, et al. (21, 22) studied the relationship of norepinephrine to heart failure and the functional state of the human myocardium. They reemphasize the role of norepinephrine in altering myocardial fiber length and contractile status as demonstrated in human left ventricular papillary muscles removed from patients at the time of mitral valve replacement.

Ayres (4) has noted products of anaerobic cardiac metabolism in dogs made ischemic by exposure to carbon monoxide. These will be presented in a subsequent section of this chapter. Weessler, et al. (156), in experiments with isolated perfused rat hearts, have reported on the importance of glucose as a substrate for anaerobic metabolism of the heart subjected to anoxia for 30 minutes. When glucose was added to the anaerobic perfusate, the electrical and mechanical performance of the heart improved markedly, as did the recovery of the heart during the subsequent period of reoxygenation. Lactate production was fivefold greater in the glucose-supported anoxic heart than in the anoxic heart without glucose. In similar fashion, morphologic changes of the mitochondria and longitudinal tubules of the anoxic heart noted by electron microscopy, were averted by the inclusion of glucose in the perfusion fluid. This experiment suggests that glucose might help temporarily to prevent myocardial infarction, caused by relative myocardial anoxia, by providing a substrate for anaerobic cardiac metabolism.

The isolated perfused rat heart was also studied by Brachfeld, et al. (12) to determine the effects of nicotine on lysosomal, mitochondrial, and supernatant enzyme systems of the myocardium. They suggested that nicotine toxicity may be expressed in terms of damage to the

lysosomal membrane and the cell wall. Shibata, et al. (132) studied the action of nicotine on the transmembrane potential and contractility of isolated rat atria. They suggest that while nicotine may influence membrane electrodynamics, there may also be a direct action on the contractile mechanism of the cardiac muscle cell by changing the duration of the action potential, which implies alterations in potassium fluxes.

Nicotine-induced changes, in dogs, in action potentials and conduction depression, with enhancement of Purkinje fibre "automaticity," may lead to the development of ventricular fibrillation (50). Post myocardial infarction dogs were much more sensitive to the administration of nicotine, as measured by electrocardiographic changes, than were normal dogs, especially in the acute stage of myocardial infarction (6). Webb, et al. (154) state that changes in fibrillation thresholds after cigarette smoking noted in dogs, by analogy, "may have relevance to the higher incidence of coronary deaths without increased incidence of angina in cigarette smokers."

#### *Studies in Humans*

The 1967 report noted that sudden death from previously undetected coronary heart disease appeared to occur frequently among cigarette smokers. Kuller (94) showed in a study of sudden death in Baltimore that arteriosclerotic heart disease was a major cause (61.4 percent) of death. No smoking histories were recorded. Luke, et al. (99) reviewed 275 consecutive autopsied cases of sudden unexpected death from natural causes, in individuals age 20 to 45 years, and noted that asymptomatic coronary artery disease comprised 28 percent of the causes of sudden death. Again, no smoking data were taken. Data pooled from 10 studies available to Burch, et al. (17), indicated that cardiovascular disease accounted for 51 percent of 8,151 adult sudden deaths.

Present clinical evidence indicates that ventricular asystole or fibrillation may be the mechanism of sudden cardiovascular death in most cases. It is known that hypoxia, hypercapnia, ischemia, electrolyte disturbances, and increased catecholamine activity all can predispose to ventricular fibrillation. From available physiological evidence noted elsewhere in this and the bronchopulmonary chapter, and also in the 1967 Report, it would appear that smoking can directly or indirectly contribute to the development of these predisposing conditions. It is well accepted clinically that ventricular, nodal, or atrial premature contractions can be increased or induced by cigarette smoking, as well as by other factors, and can be reduced by the cessation of cigarette smoking in both normal and ischemic hearts. These premature contractions are frequently precursors of their respective tachycardias. Also, a person with an acute or impending myocardial infarction subjected to the sympathoadrenal effect of smoking could

more readily develop a fatal arrhythmia (75). The relationship of smoking to cardiac arrhythmias must be studied further to determine more exactly both the physiology and the mechanisms involved in sudden deaths from cardiovascular disease.

Kerrigan, et al. (74) studied cardiac output in both smokers and nonsmokers who had no evidence of coronary heart disease and found rises in cardiac output in response to exercise and to cigarette smoking separately and then in combination. They note that the total increase in cardiac output appears to be the sum of the exercise and the smoking effects. Smoking may create an additional myocardial tissue oxygen demand above and beyond the demand attributable to exercise.

Moses, et al. (105) reported that pretreatment of healthy normals with glucose blocks the increased cardiac output response to cigarette smoking by inhibiting the increases in stroke volume but not heart rate.

Frankl, et al. (42) noted that after 5 normal male chronic smokers were given propranolol, cigarette smoking caused a significant increase in systemic blood pressure and a significant decrease in cardiac output. Thus cigarette smoking after propranolol administration may be especially hazardous. Yamamoto noted similar results (160).

Sen Gupta, et al. (130) studied 11 ischemic cardiac patients and 14 healthy controls for abnormal ECG changes after smoking one cigarette and noted specific or nonspecific changes in almost all of the cardiac patients as compared to few changes in the healthy smokers and no abnormalities in the healthy nonsmokers. Pentecost, et al. (117) studied the acute effects of cigarette smoking in patients with angina or post-myocardial infarction as compared with normal controls. Normal men and those with angina in the absence of infarction behaved similarly with an increase in pulse rate, mean pressure, stroke volume, and cardiac output. The majority of the patients among the post-myocardial infarction group showed a marked fall in stroke volume and cardiac output while smoking. In another study (43) to evaluate the interrelationship of smoking and exercise effects on cardiac output, a fall in cardiac output that occurred in some post-infarction coronary patients as a result of smoking alone was noted. Also noted were decreases in cardiac output after smoking and exercising as compared to post-exercise cardiac output in the same patients before they smoked.

Starr (139) suggests that the ballistocardiographic (BCG) findings in cardiac disease and after cigarette smoking may provide valuable information about the rate of acceleration of myocardial contractile velocity that cannot be determined by studying cardiac output or stroke volume alone. A diseased heart has a slower accelerative rate of contraction. BCG abnormalities have frequently been

related to cigarette smoking in subjects with or without heart disease, including angina pectoris. The BCG findings of Jackson, et al. (68) indicate that cigarette smoking itself may have acute and chronic harmful effects on myocardial function, since duration of smoking was also correlated with certain abnormalities.

Gazes, et al. (47), Braunwald, et al. (13), and Klensch, et al. (91) have found higher plasma norepinephrine levels in coronary patients at rest and after smoking as compared to normals. Kersibaum, et al. (77) have reported that the rise in free fatty acids after cigarette smoking is also greater in patients with coronary heart disease, probably due to an enhanced norepinephrine response.

Burch, et al. (16) also stress the importance of the action of norepinephrine on the venous vascular system. "Greater than 70% of the blood volume is contained within the systemic venous system and a 10% reduction in venous capacity would result in the sudden shifting of 350 ml. of blood (assuming a blood volume of 5 L.) centrally into the pulmonary veins and atria. In the presence of a diseased left ventricle, such a sudden increase in central blood volume may result in acute left ventricular failure" (17). (Additional cardiopulmonary considerations are noted in the bronchopulmonary disease chapter of this Report).

#### *Human Myocardial Tissue Function in Relation to Anoxia and to Carbon Monoxide*

Likoff, et al. (98) suggest that an oxygen-diffusion impairment or inappropriate oxygen utilization at the myocardial microcirculatory or cellular level could be responsible for the anginal symptoms and ECG signs of apparent myocardial ischemia in the presence of adequate arterial saturation and patent coronary arteries by coronary arteriography. Ayres (4) and Eliot (33) suggest that these mechanisms may be related to the carbon monoxide effect and abnormal hemoglobin function.

In addition to a review of the coronary circulation as related to myocardial ischemia and angina pectoris, Elliott, et al. (35) studied zonal myocardial ischemia (60) by ECG, coronary angiography and regional lactate metabolism in 50 patients with proven coronary heart disease. They found that the ECG findings could be normal even when severe coronary disease was present with myocardial production of lactate. The regional lactate pattern was very helpful in determining the location of myocardial ischemia and significant coronary artery lesions.

In studies of coronary patients exposed to relatively low levels of carbon monoxide, Ayres (4) has reported that myocardial lactate and pyruvate extraction decreased or shifted to actual production, suggesting the presence of anaerobic metabolism. These data support his

previous findings noted in the 1967 report that carboxyhemoglobin can interfere with oxygen delivery to the myocardium to the degree that relative myocardial anoxia can occur. The shift to anaerobic cardiac metabolism, which is relatively ineffective as a source of energy, indicates the presence of myocardial anoxia, and should be regarded as a warning sign. In these same experiments Ayres has noted that the myocardial oxygen extraction is decreased in response to carbon monoxide inhalation, and thus has further demonstrated the relationships of carbon monoxide with relative myocardial anoxia and anaerobic myocardial metabolism. The shift to the left of the hemoglobin-oxygen dissociation curve, describing the decreased ability of hemoglobin to release oxygen at the tissue level, is directly related to increased carboxyhemoglobin levels.

The animal experiments of Weissler (156), noted in the previous section, suggest that glucose might possibly help to temporarily prevent myocardial infarction from relative myocardial anoxia, by providing a substrate for anaerobic metabolism. Since myocardial ischemia may be caused not only by complete coronary arterial obstruction, but also by increased myocardial tissue oxygen demand above and beyond available oxygen supply, it would be important to know whether cigarette smokers have more products of anaerobic myocardial metabolism than do nonsmokers.

Eliot (34) has noted apparent hemoglobin abnormalities in patients with signs of myocardial ischemia or acute necrosis, and in smokers as compared to controls. However, he suggests that there are other hemoglobin abnormalities also present besides the well documented carboxyhemoglobin abnormalities associated with the carbon monoxide effect of cigarettes. Some reverted to normal hemoglobin status after stopping smoking.

Anomalous hemoglobin-oxygen dissociation was noted in "heavy" cigarette smokers (more than one pack per day) without known coronary heart disease. In experiments where the amount of cigarette smoking was controlled, there appeared to be a threshold effect: more than 12 cigarettes per day caused this anomalous dissociation to occur (53). Birnstingl (9) reports finding an increased hemoglobin affinity for oxygen in smokers, which does not appear to be explained solely by the increased carboxyhemoglobin levels in smokers.

Research to further study the interrelationships of carbon monoxide to the myoglobin of heart muscle should be performed because it is possible that carbon monoxide may replace oxymyoglobin with carboxymyoglobin and disturb the oxygen-dissociation phenomena of myoglobin (88, 126, 159). The limitations of blood supply and the high energy output of heart muscle as compared to skeletal muscle may make the myoglobin impairments by carbon monoxide of possible etiologic importance in cigarette smoking and heart disease.

Hydrogen cyanide appears to be rapidly converted to thiocyanates by the body, but the absorption by the lung of cyanide from cigarette smoke might possibly result in higher serum cyanide levels in the coronary arteries than in the systemic circulation. As noted in the 1964 Report, the cyanide ion is capable of stopping cellular respiration abruptly through inactivation of cytochrome oxidase. In sublethal exposures, the cyanide ion is gradually released from its combination with the ferric ion of cytochrome oxidase, converted to thiocyanate ion and excreted in the urine. Thiocyanate blood levels in smokers are three times higher than in nonsmokers and relative differences in urinary excretion are even more pronounced. Cytochrome oxidase is very important in cellular respiration of all body cells. In view of the extremely high myocardial cellular needs for aerobic metabolism, it is possible that the cyanide ion inactivation of cytochrome oxidase also can occur in myocardial cells and be of critical importance, especially in light of other risk factors such as impaired coronary blood flow, the carbon monoxide effect, and the known increases in myocardial tissue oxygen demand caused by the smoking/nicotine-induced catecholamine release. Further research is needed to determine whether or not cyanide ions in concentrations equivalent to those found in cigarette smokers, have a harmful effect on the myocardium, in terms of both acute and chronic exposures.

#### *Glucose Metabolism and Possible Cardiovascular Effects*

Epstein (37) has reviewed the relationships of hyperglycemia to coronary heart disease. Although he states that there appeared to be no relationship of cigarette smoking to the hyperglycemia that was associated with the prevalence of coronary heart disease in the Tecumseh population, Higgins (63) reports that the Tecumseh cigarette smokers, both male and female, had approximately a 10 mg. percent elevation in blood glucose as compared to nonsmokers, although the percentage elevations above the median levels were not statistically significant. Since Epstein (39) reported that cigarette smokers in the Tecumseh study population had a higher incidence of coronary heart disease, it would be interesting to see what the interrelationship of the incidence of coronary heart disease is to the cigarette smokers who have elevated blood glucose levels.

Cohen, et al. (24) have reported abnormal glucose tolerance in some postinfarction patients, suggesting the possibility that this group has difficulty utilizing glucose. It is known that smoking induces release of catecholamines which can create an increased demand for glucose by the body. Wahlberg (152) had noted that in patients with atherosclerotic disease but without clinical diabetes mellitus, the glucose tolerance was pathologic in 46 percent as compared with 10 percent of controls, and normal in 33 percent as compared with 71 percent

controls. From this he infers that subclinical diabetes mellitus may predispose to vascular disease in the same way as clinical diabetes mellitus.

Kingsbury, et al. (89) studied a small group of male patients with peripheral arteriosclerotic disease to determine the serum glucose, non-esterified fatty acids, and immunoreactive insulin responses to subcutaneous adrenaline and to smoking. Under basal conditions, the fatty acid response was normal. While adrenaline consistently caused a rise in serum glucose, cigarette smoking either had no effect or lowered the fasting concentration. In 5 patients smoking caused an elevation in the immunoreactive insulin which could not be explained by blood sugar changes. The implication is that these patients were hypersecretors of insulin. Unfortunately, detailed smoking histories are not available for these individuals. Szanto (141), in a very small study of habitual smokers, noted a "hyperinsulinism" response during oral glucose tolerance testing after smoking two cigarettes. This response was markedly reduced when the test was repeated after a 14-day abstinence from smoking. The view that hyperinsulinemia is associated with atherogenesis has been suggested (114, 118, 149, 157) and discussed by Mahler (102). If smoking directly or indirectly causes a hyperinsulin response in some individuals, then this may possibly be one mechanism by which cigarette smoking may enhance atherogenesis.

Kershbaum, et al. (86) have noted higher plasma 11-hydroxy corticosteroid levels in smokers. Whether the "hyperinsulinism" reported to be present in smokers is related to increased adrenal corticosteroids remains to be determined. Hyperinsulinism could be a response to the frequent catecholamine-induced hyperglycemia caused by cigarette smoking in individuals without significant clinical or subclinical coronary heart disease; but conceivably the hyperinsulinism response might be more pathological in coronary patients. Also, the potassium and other ion changes caused by glucose shifts in response to shifts in insulin levels may predispose to cardiac arrhythmias and sudden death.

#### *Additional Considerations Regarding Coronary Blood Flow*

Coronary blood flow, besides being influenced by the size of the inner lumen of the coronary vessel wall and its ability to dilate for the purpose of increasing flow of oxygenated blood when needed by heart muscle, is also dependent upon the viscosity of the blood (16). The concepts of fluid mechanics, such as laminar or turbulent flow, are well known. For any given aperture and pumping pressure, fluid flow will depend somewhat upon the physical characteristics of the fluid itself. It has been demonstrated in both cigarette smokers (100) and in patients with myocardial infarction that hemoconcentration occurs (15, 137), sometimes to a relatively small degree in terms of absolute changes in hematocrit, but the changes in viscosity are much greater

than might have been predicted from consideration of hematocrit changes alone. At this point, other factors related to fluid mechanics also enter in, such as the quality and amount of lipids in the blood. Burch, et al. (15) have demonstrated that increased fatty acids increase the force necessary to "shear" the blood, thus contributing to a reduction in the capacity of the blood to flow in laminar fashion through a given aperture. When coronary arteries are impaired by partial obstruction of the inner lumen or by decreased distensibility, there may be a critical interaction with blood viscosity causing marked turbulence of flow and thus reducing further the potential for increasing coronary blood flow.

#### SUMMARY. CONCEPT AND CONCLUSION

Additional evidence has been presented which tends to confirm and extend the positive findings previously reported in the 1964 and 1967 reports.

1. Epidemiological studies show that "heavy" cigarette smoking is strongly associated with an increased risk of dying from coronary heart disease.

2. New data confirm and help to clarify the relationship between cigarette smoking and other "risk factors" in the development of coronary heart disease suggesting that both independent and interacting effects are involved.

3. Evidence indicates that cigarette smoking may accelerate the pathophysiological changes of pre-existent coronary heart disease and contribute to sudden cardiovascular death. This relationship helps to explain why stronger epidemiological correlations between cigarette smoking and coronary heart disease tend to be found in incidence studies rather than in prevalence studies where the population is under-represented for those people who have had fatal outcomes from coronary heart disease.

4. Present evidence continues to support the position that giving up cigarette smoking is beneficial to cardiovascular health.

5. Some progress is being made in the study of the interrelationships of selected psychological factors, smoking behavior, and the development of coronary heart disease.

Recent data provide a basis for the formulation of a theoretical concept by means of which it is possible to correlate the interaction of several known coronary heart disease risk factors with the physiological mechanisms by which cigarette smoking may affect the myocardium.

The epidemiological studies continue to indicate that "heavy" cigarette smoking is strongly associated with a fatal outcome from coronary heart disease. This fact may be accounted for by a mechanism



whereby, in the presence of impaired coronary circulation due to coronary heart disease, cigarette smoking may "trigger" myocardial oxygen deficits of critical degree. One or more of the following mechanisms may be involved in this process:

1. The increase of myocardial wall tension and velocity of contraction, largely mediated through norepinephrine released in response to cigarette smoking, thereby increasing the myocardial demand for oxygen and other nutrients.

2. The relative reduction of nutrient capillary blood flow in the region of the myocardium distal to and dependent upon blood flow through a partially occluded coronary artery.

3. The impairment of oxygen dissociation from hemoglobin due to the formation of carboxyhemoglobin from carbon monoxide, thereby diminishing the availability of oxygen to the myocardium.

4. The reduction of the supply of oxygen available to the myocardium as a consequence of hypoxemia due to severely impaired pulmonary function from chronic obstructive bronchitis.

5. The impairment of coronary blood flow as a result of the increased blood viscosity associated with hyperlipemia or hemoconcentration.

6. The increase in platelet adhesiveness which might contribute to thrombus formation or coronary occlusion.

7. The predisposition to acute cardiac arrhythmias as a consequence of harmful neurogenic reflexes or catecholamine release.

8. The possible, although presently speculative, contributions to impairment of myocardial cellular respiration by cyanide ion.

Thus, the interaction of the factors which decrease oxygen supply to the myocardium and those which increase the myocardial demand for oxygen may play a major role in precipitating the fatal outcome in some individuals with coronary heart disease. On the other hand, it is possible that the same factors, in less severe clinical circumstances, could precipitate temporary coronary insufficiency or contribute to nonfatal myocardial infarctions or cardiac arrhythmias.

The pathophysiological factors associated with cigarette smoking may further interact with other known epidemiological risk factors associated with coronary heart disease such as high serum cholesterol and high blood pressure. Although not a "risk factor", unusually high physical stress may also create physiological demands for additional oxygen supply to the myocardium.

The finding that those who discontinue cigarette smoking have a lower risk of dying from coronary heart disease than those who continue to smoke might be accounted for by the potential reversibility of many of the pathophysiological effects of smoking on the cardiovascular system. It is reasonable to expect partial reversibility of factors that interfere with oxygen supply, such as the carbon monoxide

effect, and the increased platelet adhesiveness, hyperlipemia, and hemoconcentration noted in cigarette smokers. Moreover, the increased myocardial oxygen requirements associated with the cigarette smoking-induced catecholamine response and neurogenic reflexes could be expected to be eliminated upon cessation of cigarette smoking. In some patients, the cardiopulmonary benefits of stopping smoking may reduce pulmonary hypertension.

An increased ability to predict future cardiovascular events in individual persons will depend upon more precise definition and measurement of the pathophysiologic factors associated with cigarette smoking and their correlation with information about the epidemiological risk factors.

Because of the increasing convergence of epidemiological and physiological findings relating cigarette smoking to coronary heart disease, it is concluded that cigarette smoking can contribute to the development of cardiovascular disease and particularly to death from coronary heart disease.

### SMOKING AND CEREBROVASCULAR DISEASES

Many of the pathophysiological considerations noted in the above section may also pertain to the relationship of smoking and cerebrovascular disease.

A mortality study in Japan by Hirayama (65) reports findings different from those cited in the 1967 Report (146), in which smokers under age 75 had a mortality ratio of 1.40, or more, for stroke.

Hirayama found that deaths due to vascular lesions of the central nervous system, after age 40, were one-third less frequent among smokers than among nonsmokers. Several factors may account for these different findings. One is that the etiologic spectrum for stroke in Japan includes more hemorrhagic strokes than in the United States. Another is that the Japanese study included all stroke deaths over age 40, whereas the studies in the United States found the positive association between smoking and stroke mortality occurred under age 75 (54).

In a study reported by Kuhn (93), 20 habitual smokers refrained from smoking for one-half day and baseline retrograde brachiocerebral angiograms were taken; then they smoked one cigarette, inhaled deeply, and had repeat angiograms. Only those over 60 years of age failed to have significant acceleration of flow in cerebral precapillary vessels and markedly increased vessel counts as in carbon dioxide inhalation experiments.

As in coronary heart disease, it may be that smoking has different effects depending upon the degree of underlying arteriosclerotic disease present. Among patients with stroke, many have arteriosclerotic heart disease and a significant number die of myocardial infarcts (104).

The rate of oxygen uptake in the brain is very high, being approximately 5 cc. oxygen/100 g. brain/min. (104). As discussed in the cardiovascular section, if carbon monoxide causes a shift to the left in the oxygen hemoglobin dissociation curve, it would make less oxygen available to the brain tissue. Those people with an arteriosclerotic cerebrovasculature who cannot increase their cerebral blood flow in response to smoking may therefore more easily develop a state of relative cerebral hypoxia; a situation which could be a factor in the etiology of stroke.

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## CHAPTER 2

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### Smoking and Chronic Bronchopulmonary Diseases (Non-Neoplastic)

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## INTRODUCTION

The primary purpose of the 1968 Supplemental Report is to review the pertinent literature that has become available subsequent to the 1967 report. Brief mention of the conclusions of the 1964 report and the highlights of the 1967 report is made to facilitate an understanding of the significance of the newer information. The current research findings should be considered in the perspective of the research evidence previously reported in the 1964 (59) and 1967 (57) reports.

### CONCLUSIONS OF THE 1964 REPORT (59)

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

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

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

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

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

6. Cigarette smoking does not appear to cause asthma.

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

### HIGHLIGHTS OF THE 1967 REPORT (57)

1. New data confirm and to some extent strengthen the conclusions of the Surgeon General's 1964 Report.

2. Cigarette smoking is the most important of the causes of chronic non-neoplastic bronchopulmonary diseases in the United States. It greatly increases the risk of dying not only from both chronic bronchitis but also from pulmonary emphysema.

3. Cessation of smoking is followed by a reduction in mortality from chronic bronchopulmonary disease relative to the mortality of those who continue to smoke.

4. Even relatively young cigarette smokers frequently have demonstrable respiratory symptoms and reduction in ventilatory function.

#### GENERAL BRONCHOPULMONARY DISEASE MORTALITY AND MORBIDITY

The 1967 report (57) pointed out the alarming rate of increase in emphysema and/or chronic bronchitis mortality (table 1). There were 25,416 deaths from emphysema and/or chronic bronchitis in 1966 which represent a 25 percent increase over 1964. The increasing death rates for chronic bronchitis and emphysema since 1950 are shown in figure 1. Death rates for these diseases are increasing more rapidly than are the death rates for lung cancer as illustrated in figure 2.

Last year, payments made by the Social Security Administration to men and women totally disabled because of emphysema amounted to about 90 million dollars; this was 7 percent of all disability payments, making chronic lung disease second only to heart disease in this regard.

TABLE 1.—Mortality from emphysema and/or chronic bronchitis: United States, each year 1950-1964

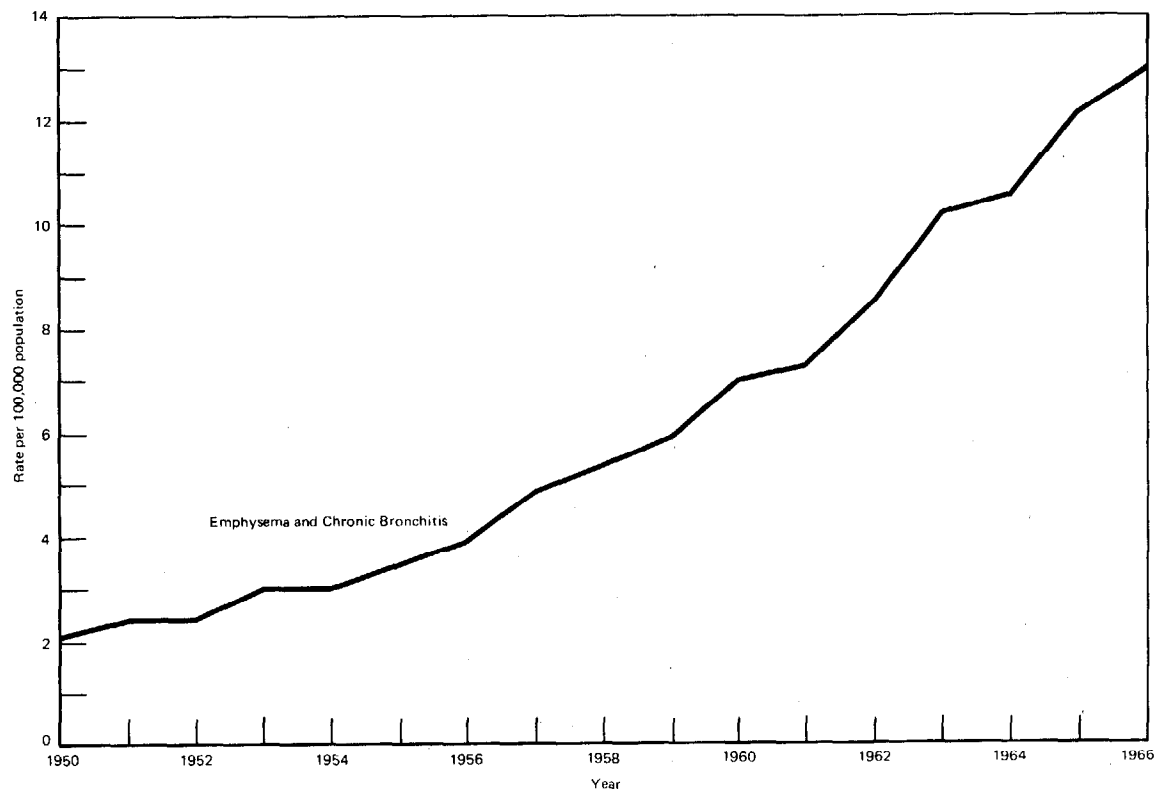
[ISC codes 501, 502, 527.1]

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

SOURCE: Vital Statistics of the United States, 1950-1964 (58).

#### POPULATION STUDIES

Several papers published in the past year reported the results of surveys of pulmonary function and respiratory symptoms in different populations. All of those which were reviewed and which included a comparison of findings between smokers and nonsmokers reported similar observations. In all instances, smokers had respiratory symptoms such as cough, phlegm production, and dyspnea more often than nonsmokers or ex-smokers of the same age and sex. In surveys which included pulmonary function tests, it was found that smokers did not perform as well as nonsmokers or ex-smokers. Substantially, these observations confirm those of earlier years without indicating new associations.



**FIGURE 1—Death rates for emphysema and chronic bronchitis. United States, 1950–1966 (Arithmetic scale).**  
**SOURCE: National Center for Chronic Disease Control.**

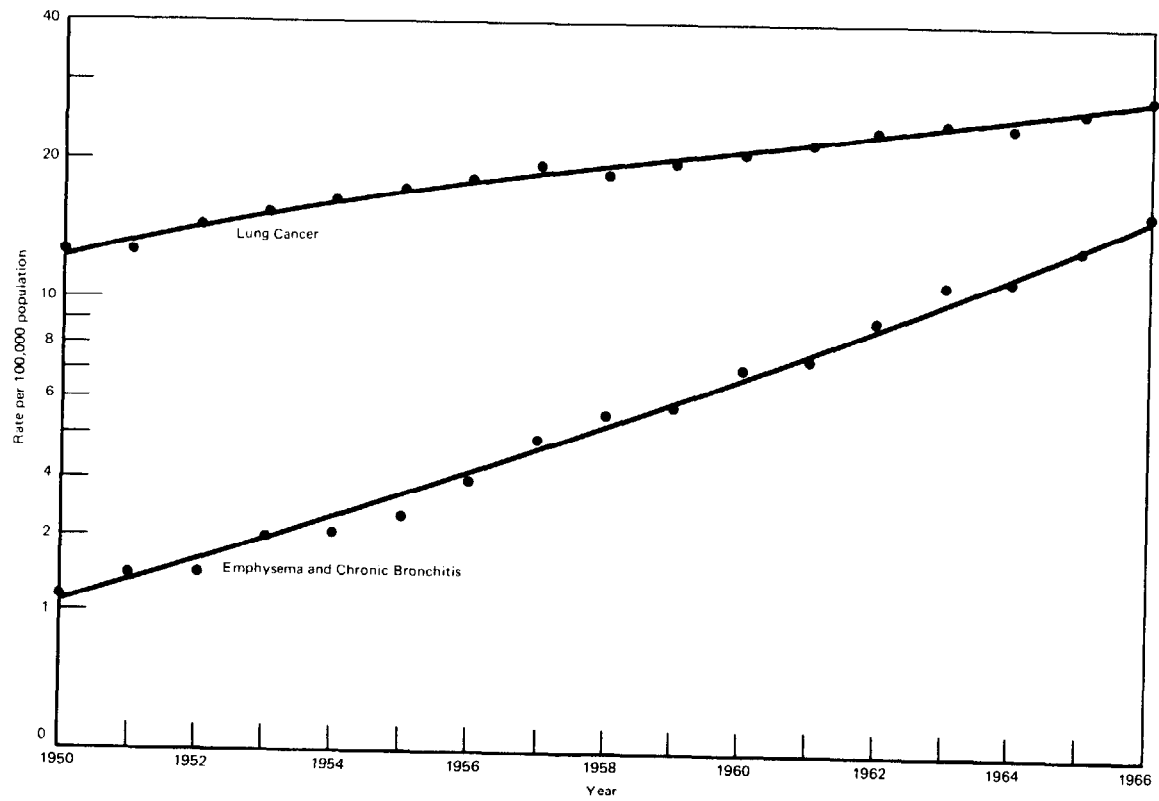


FIGURE 2—Death rates for emphysema and chronic bronchitis and for lung cancer: United States, 1950-1966 (Logarithmic scale).  
SOURCE: National Center for Chronic Disease Control.



A few specific surveys might be mentioned. Huhti (27) surveyed 1,028 men and women in a village in Finland. None of the women smoked. In men the one-second forced expiratory volume ( $FEV_{1.0}$ ) and the peak expiratory flow (PEF) were significantly lower among those men who smoked 15 or more cigarettes a day than those who smoked less or not at all. No difference in forced vital capacity (FVC) was observed.

Edelman, et al. (14) studied 410 men and found lower values of  $FEV_{1.0}$ , FVC, and maximal voluntary ventilations among current smokers than among nonsmokers. They also reported an inverse relationship between the number of cigarettes smoked and pulmonary function.

Stanek, et al. (54) noted a definite association between chronic cough and phlegm production (chronic bronchitis) and cigarette smoking among a random sample of 443 men surveyed in Prague. Freour, et al. (21) in Bordeaux also reported a much greater frequency of symptoms of chronic bronchitis among smokers than nonsmokers in a preliminary report based on 1,055 examinations.

Higgins and his associates (25) reported observations from a nine year followup study of men in an industrial town in England. Among the 385 men who were age 55-64 at the start of the study, mortality during the nine years was twice as high for smokers as nonsmokers. Ex-smokers had the same mortality experience as nonsmokers. Among the survivors of all ages who were tested initially and nine years later, the average decline in lung function as measured by the  $FEV_{0.75}$  was smallest in nonsmokers, slightly greater in ex-smokers, and greatest in smokers. The findings suggested that smoking was a more important factor than occupation in respiratory disability.

Industrial air pollution studies have been performed by Lowe (32) using a population of steelworkers at Ebbw Vale and Port Talbot, with smoking and chronic bronchitis data presented in a subsequent publication (31). It was noted that for each age group, chronic bronchitis was about three times more prevalent among men who smoked 25 or more cigarettes per day, than among those who had never smoked. Cigarette smokers appear to be more adversely affected by pulmonary exposure to dusts at work than the nonsmokers. The authors pointed out that studies to evaluate the interaction between smoking and industrial air pollution require occupational subgroups large enough to permit standardization for both age and smoking habits. In this way, the interaction between smoking and other air pollutants can be analyzed more definitively.

Most surveys have been of adults, but Holland, et al. (26) reported the findings of an investigation of smoking and respiratory symptoms among more than 10,000 school children, age eleven or more, in England. The survey was conducted in 1965 and repeated in 1966. Ciga-

rette smokers (at least one cigarette per week) more frequently reported symptoms of cough and phlegm production than nonsmokers and the prevalence of symptoms increased with increases in the amount smoked. Children who smoked one year but did not smoke in the subsequent year had a lower frequency of symptoms in the second year.

#### RELATIONSHIPS TO PULMONARY INFECTION

The relationship between smoking and pulmonary infection is unclear. It is evident that cigarette smoking is a major cause of chronic bronchitis. Much of the symptomatology of chronic bronchitis of smokers, particularly cigarette smokers, results from the harmful effects of inhaled tobacco smoke on the bronchial ciliary apparatus and the mucous glands. These effects tend to impair mucous removal from the bronchial and bronchiolar airways and possibly may, in turn, increase susceptibility to pulmonary infections.

In a study of 191 boys, age 14 to 19, in a preparatory school, the incidence of all respiratory illness over a one-year period was positively correlated with smoking habits within each age group. "Severe" (purulent sputum) lower respiratory tract illnesses were nine times more frequent in regular smokers than nonsmokers (age-adjusted) (24).

A study in Cairo of the relation between smoking and infection and appearance of mucous gland hypertrophy in the main bronchi was reported by Megahed and his colleagues (34). They studied 50 men with chronic bronchitis and found substantially more mucous gland hypertrophy among the 43 smokers than the 7 nonsmokers. This hypertrophy seemed unrelated to the presence of potential pathogenic organisms isolated from a single bronchial lavage, although the authors believed that infection might have an initiating or potentiating effect.

Fletcher (17) studied the relationship between frequency of respiratory illness as measured by sputum purulence and histories of "chest illnesses" and "chest colds" and the rate of decline of FEV in slightly more than 900 men who were followed at least four years. He concludes that illnesses and sputum purulence have no significant effect on FEV regression. (This study will be discussed again later in this chapter).

It appears that, in patients with chronic obstructive bronchopulmonary disease caused by cigarette smoking or other pulmonary irritants, superimposed infections may cause exacerbations of the chronic disease process. There is no substantial evidence that infections per se cause much of the chronic obstructive bronchopulmonary disease seen in cigarette smokers.

Wynder (62) reported that the hyperplastic and metaplastic effects of Swine influenza virus could not be enhanced by subsequent exposure

of mice to cigarette smoke. Previous literature indicates that the sequence of events may be of some importance, since there have been reports that cigarette smoke increases the bronchial epithelial reaction to influenza virus. Spurgash (53) reported that pre-exposure to cigarette smoke did not have any significant effect on resistance of mice to subsequent influenza virus infection inoculated by aerosol inhalation. But, the subsequent exposure of pre-infected mice to cigarette smoke resulted in significantly higher mortality rates, thus suggesting that cigarette smoke can aggravate an existing respiratory viral infection. However, smoke-exposed mice subsequently challenged with certain bacteria, *Klebsiella pneumoniae* or *Diplococcus pneumoniae*, also exhibited a decreased resistance to respiratory infection as shown by a decreased survival time and a higher mortality (53).

The tobacco plant can be diseased by a variety of fungi (33). Of these the *Alternaria* species and *Aspergillus niger* were recently shown to increase the toxicity of cigarette smoke (20). Mice exposed to smoke from hay previously inoculated with *Alternaria* or *Aspergillus niger*, showed progressive pulmonary congestion, edema and tissue destruction confirmed by autopsy. Those mice in a hay-smoke control group were normal clinically and showed only chronic pulmonary inflammation on autopsy.

## SMOKING AND BRONCHOPULMONARY PHYSIOLOGY

### ANIMAL AND EXPERIMENTAL STUDIES

The ciliotoxic effects of cigarette smoke were presented in the 1964 (59) and 1967 Reports (57). Discussants in a recent symposium (29), pointed out that both volatile and particulate components of cigarette smoke can adversely affect ciliary activity. In short-term *in vivo* experiments, Dalhamn (11) showed that the ciliostatic effect of cigarette smoke was directly related to the "tar" content if the gas phase was held constant.

Rylander (44) reported that in guinea pigs exposed to cigarette smoke, the reduction of killed, radioactive bacteria was lower than in controls, presumably due to a decrease in mucus flow. There was no significant difference in reduction of viable bacteria.

A study by Dalhamn, et al. (10) suggests that lack of oxygen in the external environmental *in vitro* can reduce ciliary activity. The main problem in the evaluation of studies related to ciliary activity is to determine to what extent the *in vitro* studies can relate to the *in vivo* studies in animals and in man. For instance, the ciliotoxic effects of hydrogen cyanide in cigarette smoke were dose-related in experiments on clam gills *in vitro*, but the same results could not be reproduced with *in vivo* experiments in cats (12). Volatile (gas phase) components have been shown to be retained to a large extent by wet surfaces (28),

which raises the question of how much of the volatile ciliotoxic agents in cigarette smoke entering the moist oral cavity actually enter the lower respiratory tract.

Davis, et al. (13) in experiments with respiratory irritants including cigarette smoke in guinea pigs, have implicated the nasopharynx and larynx as sources of receptor stimulation leading to increased upper airway resistance, and decreases in respiration rate and minute volume. These effects were not present when a tracheostomy was performed to bypass the smoke directly into the trachea. However, Guillerm (23) noted increased airway resistance and decreased compliance in the tracheotomized and spinal guinea pig after smoke inhalation.

Aviado and his co-workers (2, 3, 4, 19, 38, 45, 46, 47, 48) have continued their studies on bronchoconstriction and bronchodilation in animals and recently have further investigated the role of histamine in a study of inhibitors for histamine decarboxylase in rabbits, dogs, and cats (39). These species have variations in response to cigarette smoking as previously noted. Cats have a uniphasic bronchoconstrictor response to inhaled cigarette smoke (somewhat like man's) and dogs have a biphasic response. Rabbits were observed to behave differently than cats or dogs. Histamine has been implicated as mediating part of the bronchoconstrictive effect of cigarette smoke. The rabbit does not respond to histamine by bronchoconstriction. This study (39) suggests that the rabbit lacks a histamine sensitive system in the airways, in contrast to cats and dogs. Alpha-hydrazino histidine, which inhibits the enzyme histamine decarboxylase, was demonstrated to prevent much of the bronchoconstrictive effect in cats and dogs. By analogy, this suggests the possibility that histamine may mediate some of the bronchoconstrictive response to inhaled tobacco smoke noted in humans. Pretreatment with atropine has been shown to block the bronchoconstriction caused by cigarette smoke (36) and by histamine inhalation in humans (7, 8, 52).

There is experimental evidence (48) in dogs, that the pulmonary exposure to inhaled cigarette smoke or injected nicotine can result in pulmonary vasoconstriction, causing increased pulmonary arterial pressure. This effect is thought to be due to histamine release from lung tissue (48). Autopsy studies in humans, by Auerbach (1), showed considerably greater fibrous thickening of the arterioles and small arteries in smokers, occurring not only in the lungs, but other organs as well. The degree of fibrous thickening increased with age and the amount of cigarette smoking.

Participants in a recent international symposium on the mechanism of elimination of deposited particles from the lungs (15), discussed the relationships among alveolar surfactant, alveolar macrophages, the alveolar transport mechanisms, and the mucociliary apparatus; which may also relate to the pathoetiology of pulmonary emphysema.

Giammona (22) reports that cigarette smoke consistently lowers the maximal surface tension without altering the minimal surface tension of lung extracts after *in vitro* exposure to cigarette smoke. *In vivo* changes were noted in guinea pigs, but not in dogs or cats, which he thought may have been due to insufficient exposure. Additional information concerning surfactant has been discussed by Sekulic, et al. (49, 50). Yeager, et al, (63) have reported that cigarette smoke has a depressant effect on protein synthesis of human alveolar cells *in vitro*.

#### STUDIES IN HUMANS

Fletcher (17) in the study mentioned earlier in this chapter, correlated the rate of decline of FEV in over 900 men followed for at least four years, with respect to starting FEV, cigarette smoking, sputum purulence, and histories of respiratory infections. He tested FEV's in response to the acute effect of smoking cigarettes, and found that the mean regression of FEV in those subjects who had a higher prevalence of cough and sputum was not significantly different from those with a lower prevalence. The men with higher initial standardized levels of FEV had less steep regressions than those with lower levels. Cigarette smoking had a significant effect on decline of FEV. Sputum eosinophilia was also related but apparently to a lesser degree, and Fletcher stated that there was no confirmation of the possible role of tobacco allergy in chronic obstructive bronchitis. With regard to the decline in FEV, more information on controls and on the quantity of cigarettes usually smoked would be helpful. While contributing important information, this study does not fully describe the progression of declining FEV in cigarette smokers in relation to the quantity that they smoked before and over the time-period studied. In a detailed study of 58 bronchitics (50 of whom had positive smoking histories) Simonsson (51) found a positive correlation between the degree of obstructive status and the reactivity to exposure to nebulized acetylcholine; and noted that a larger decrease in airflow seems to occur in previously obstructed airways than in normal ones.

Peterson (42) studies pulmonary function in a group of 12 individuals who had stopped cigarette smoking for 18 months, and compared their pulmonary function test before and after cessation. These individuals showed significant improvements in their pulmonary functions as measured by timed vital capacity and expiratory flow rates. Ex-smokers reported a decrease in cough and breathlessness after cessation of smoking. (This study confirms the findings of Krumholz reported in the 1967 report). The mean FEV of Peterson's ex-smokers was markedly greater than that observed in another group of individuals who had continued to smoke cigarettes during the same 18 month period, measured at the same time intervals.

Wilhelmsen (60) found in a small study of 16 persons who had smoked over 10 cigarettes a day for a mean of 25 years that cessation of cigarette smoking for an average of 40 days was accompanied by a marked decrease of sputum production, coughing and wheezing, and a significant increase in FEV<sub>1</sub>.

Bates (5,6) has reviewed the reliability and constancy of pulmonary function tests. He notes the importance of making pathological diagnoses with lungs inflated at autopsy. Morphologic considerations of emphysema are correlated with functional abnormalities and current biochemical research. He discusses derangement of pulmonary ventilation-perfusion distribution in relation to bronchial and/or alveolar damage from cigarette smoking with consequent stresses on right ventricular function. He emphasizes the fact that obstructive bronchitis appears to lead more frequently to right heart failure than does "pure" emphysema.

Although instances of "pure" emphysema or "pure" bronchitis exist, most patients with respiratory obstruction appear to have both emphysema and bronchitis. Bates suggests the theory that one of cigarette smoking's harmful effects may be destruction of bronchiolar structure. This could lead to disturbed ventilation-perfusion (V/Q) relationships. As enough lung tissue breaks down, causing centrilobular emphysema, there is impairment of gas equilibration within the centrilobular spaces. Increasing derangement of the V/Q distribution in turn can lead to hypercapnia and hypoxemia. Clinically, what may seem to be respiratory decompensation, may actually be incipient cardiopulmonary decompensation due to the deranged V/Q and gas imbalance resulting from the obstructive bronchiolitis.

Postural hypoxemia has also been noted (55) in young asymptomatic cigarette smokers with no evidence of chronic lung disease when in the supine position as compared with nonsmoking controls.

#### THEORIES INTERRELATING CIGARETTE SMOKING AND CHRONIC OBSTRUCTIVE BRONCHOPULMONARY DISEASE WITH PULMONARY HYPERTENSION AND COR PULMONALE

Hypercapnia and hypoxemia are capable of causing pulmonary vasoconstriction with a resultant increase in pulmonary arterial pressure and right ventricular work. Stuart-Harris, in a review article (56), relates these phenomena to the clinical picture of pulmonary hypertension and right heart failure seen in patients with pulmonary insufficiency caused by chronic obstructive bronchitis. Since the pathologic changes in the small pulmonary vessels are not usually as severe as those found in congenital heart disease, it is believed that the pulmonary hypertension seen in chronic obstructive lung disease is of the vasoconstrictive type. Although most patients with severe chronic

bronchitis have some emphysema, it is the airway obstruction of chronic bronchitis which may relate most strongly to the development of *cor pulmonale*. It is now apparent that *cor pulmonale* can be a sequel to severe obstructive bronchitis without emphysematous changes (9, 17, 35, 37). Studies (16, 18, 43) indicate that patients with hypercapnia and hypoxemia due to abnormal pulmonary ventilation-perfusion relationships are likely to develop cardiac complications. As indicated in the preceding section of this report, recent studies (40, 41, 43) have demonstrated the presence of ventilation-perfusion imbalances in patients with chronic bronchitis—the extent of imbalances being related to the severity of bronchitic process. Penman, et al. (41) determined the gas tensions in expired air and arterial blood and used them to calculate the alveolar dead space and alveolar blood shunt, permitting estimation of three theoretical “compartments” of the lung: (1) Ventilated but unperfused (alveolar dead space) “compartment,” (2) unventilated perfused (alveolar blood shunt) “compartment” and (3) “normal” ventilated perfused “compartment.” Chronic bronchitis were found to have abnormalities of ventilation and perfusion with a marked reduction in the “normal” “compartment.” In patients with decompensated *cor pulmonale*, further studies of the correlations between cardiac output, arterial oxygen tension, and arterial carbon dioxide tension with the above “compartments” lead Penman, et al. (41) to believe that in cases of decompensated *cor pulmonale* a considerable fraction of the cardiac output is shunted without exposure to aerated alveoli.

It was further hypothesized that this increased shunting of blood through non-aerated regions of lung would result in increasing hypoxemia and hypercapnia with consequent further constriction of the pulmonary vasculature and further encroachment of the alveolar dead space upon the normally ventilated and perfused lung. Williams, et al. (61) in determining the acute effects of cigarette smoking, found an increase in the “alveolar dead space” in 11 patients with obstructive airway disease. They postulate this to be due to “the effect of nicotine on the vasculature of the lung in this group of patients.”

Since pulmonary vasoconstriction will also increase the pulmonary arterial pressure and right ventricular work, it may also lead to right ventricular failure and the classic picture of *cor pulmonale*. The beneficial effects of correcting (to the extent that this is possible) the ventilatory problems in these patients is well known, and it is thought that the basis of the improvement is the correction of the hypoxemia and hypercapnia which allows a reversal of the pulmonary vasoconstriction, thereby permitting better perfusion of underperfused areas and also decreasing the workload of the right ventricle. Stuart-Harris also pointed out that the relief of myocardial anoxia with appropriate therapy may help the right ventricle recompensate.

Long-term continuous oxygen therapy in hypoxemic patients with chronic airway obstruction has been noted to have a beneficial effect of reducing pulmonary arteriolar resistance (30).

It is pertinent to note at this point that there is a developing body of experimental evidence discussed in previous Reports and in this chapter that cigarette smoking may have acute deleterious effects on airway resistance and pulmonary vasoconstriction which can be especially harmful to the patient whose pulmonary function is already compromised. The disordered pulmonary ventilation-perfusion relationships and pulmonary hypertension found in some patients with severe chronic bronchitis can only be worsened by further bronchoconstriction and possibly by pulmonary vasoconstriction caused by continued cigarette smoking. These can enhance cardiopulmonary decompensation and lead to heart failure from cor pulmonale.

Further research is necessary to clarify more precisely the interrelationships between the disturbances of ventilation-perfusion caused by chronic obstructive bronchopulmonary diseases and cardiovascular abnormalities as they relate to cigarette smoking.

#### SUMMARY AND RESEARCH SUGGESTIONS

Additional evidence compiled since 1967 confirms previous positive findings and extends our knowledge about some of the effects of cigarette smoking on pulmonary function. There has been further clarification of some of the interrelationships between chronic obstructive bronchitis and adverse cardiopulmonary effects indicating that pulmonary hypertension and cor pulmonale may result from the more severe forms of chronic obstructive bronchopulmonary disease. Smoking is a major cause of chronic bronchopulmonary disease and in addition may have particularly harmful cardiopulmonary effects in those patients with severe chronic obstructive bronchitis.

Research suggestions: (1) Long-term followup studies on changes in pulmonary function among continuing cigarette smokers as compared to those who have never smoked cigarettes and those who have discontinued cigarette smoking. (2) Longitudinal studies of relatively young people prior to the initiation of smoking in order to compare pulmonary function before and after the taking up of smoking.

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## CHAPTER 3

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# Smoking and Cancer

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## INTRODUCTION

The primary purpose of the 1968 Supplemental Report is to review the pertinent literature that has become available subsequent to the 1967 Report. Brief mention of the conclusions of the 1964 Report and the highlights of the 1967 Report is made to facilitate an understanding of the significance of the most recent information.

The current research findings should be considered in the perspective of the research evidence previously reported in the 1964 (91) and 1967 (92) Reports.

### CONCLUSIONS OF THE 1964 REPORT (91)

#### *Lung Cancer*

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

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

3. The risk of developing cancer of the lung for the combined group of pipe smokers, cigar smokers, and pipe and cigar smokers is greater than for nonsmokers, but much less than for cigarette smokers. The data are insufficient to warrant a conclusion for each group individually.

#### *Oral Cancer*

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

2. Although there are suggestions of relationships between cancer of other specific sites of the oral cavity and the several forms of tobacco use, their causal implications cannot at present be stated.

#### *Laryngeal Cancer*

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

#### *Esophageal Cancer*

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

#### *Cancer of Urinary Bladder*

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

### *Stomach Cancer*

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

## HIGHLIGHTS OF THE 1967 REPORT (92)

### *Lung Cancer*

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

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

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

### *Laryngeal Cancer*

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

### *Other Cancers*

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

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

## GENERAL ASPECTS OF CARCINOGENESIS

Since the 1967 report, recent advances in the tobacco chemistry field were reviewed in two articles (65, 82). The characterization of tobacco smoke by gas chromatography and digital computer opened a new avenue for the exploration of tobacco smoke. The first preliminary data indicate the presence of several thousands of compounds in tobacco smoke. This number far exceeds the 700-800 compounds presently identified (23).

The 1967 Report discussed the major concepts of experimental tobacco carcinogenesis. A recent monograph by Wynder and Hoffmann (104) thoroughly describes and analyzes experimental carcinogenesis as it relates to tobacco and tobacco smoking. The reduction of tumorigenicity is of particular concern. This can be accomplished by: (1) reduction of total "tar" content, and (2) reduction of specific tumori-

genic agents. It has been well established that experimental tumor production is dose-related to the amount of "tar" in cigarette smoke condensate (7). The amount of "tar" yield varies with parameters such as: (1) type of tobacco, (2) curing and processing, and (3) filtration. It has been demonstrated that by selecting, curing and blending as well as by using specific filter materials and cigarette paper, one can significantly reduce the "tar" yield of mainstream cigarette smoke (29, 83, 88).

Over the past 15 years there has been a general decrease in the amount of "tar" and nicotine content of cigarettes (96, 104). One reason probably is the decreased nicotine and "tar" content in the "lighter" tobaccos now being grown. Another is the increased public demand for "filtered" cigarettes.

Increased nitrate content of tobacco and the addition of nitrate to cigarettes has been reported to reduce the tumor yield in experimental animals (104). Smoke from air-cured tobacco is less tumorigenic than flue or sun-cured tobacco (96, 104) and cigarettes using more sheets and stems rather than whole leaf have been shown to be less tumorigenic (64, 104).

Also, more porous cigarette paper (70), and the addition of nitrate, citrate, or phosphate to cigarette paper increases the burning rate of the cigarette, thereby lowering the number of puffs taken per unit of cigarette (104).

Filtration will decrease the total "tar" yield (61, 63, 96, 104), but except for the phenolic component, commercial filters do not selectively filter specific carcinogenic components from the "tar".

It has been shown that "tars" of tobacco extracts have increasing carcinogenic properties in direct relationship to the temperature of pyrolysis (104).

It is important to note that tobacco extract itself contains relatively high amounts of tumor promoters. The tumor promoting activity of tobacco extracts is of the same magnitude as that of tobacco smoke condensate (104) but so far no clear tumorigenic relationship is evident between them (6).

#### N-NITROSAMINES

Despite recent publications on the presence of N-nitrosamines in tobacco (76) and cigarette smoke (55), the present evidence must be regarded as insufficient because of the high probability that this is artifactual (66). The studies described so far have failed to identify these agents in fresh tobacco smoke (45, 66). However, since several of the N-nitrosamines are strong carcinogens (58) and tobacco smoke contains several dozen secondary amines and oxides of nitrogen which may be precursors for nitrosamines (66, 76, 80, 105), tobacco smoke should be regarded as a potential source of N-nitrosamines.

## POLONIUM-210

New data on polonium-210 in tobacco leaf and cigarette smoke have originated from various countries (8, 13, 26, 27, 28, 51, 52, 68, 89). The polonium-210 values vary between 1-50 picocuries per 1.0 g. tobacco; 30-50 percent of it is recoverable in the mainstream smoke of cigarettes without filter tips. Using special filter material, up to 90 percent of the polonium-210 can be filtered out of the mainstream smoke (8). One major source for polonium-210 in tobacco was reported to be phosphate fertilizer (89). Analyses of human tissues demonstrated that lung, blood, and liver of smokers contain higher concentrations of polonium-210 than the corresponding organs of nonsmokers (27, 40, 41, 57, 68). Rajewsky et al. (68) estimate a daily polonium-210 inhalation rate of 2 picocuries for a smoker of 20 cigarettes per day. Their autopsy studies indicate an alpha dose exposure for the basal cells of the subsegmental and terminal bronchi of 41 mrem and 79 mrem per year, respectively, in smokers of 20 cigarettes per day. In view of the fact that Jacobi (44) calculated a dose rate in these same basal cells of 1-2 rem per year from the decay of naturally occurring radon and thoron in the air, Rajewsky, et al. (68) consider it unlikely that cancer is caused by the inhalation of polonium-210, in tobacco smoke. In a review of the role of radioactive substances on the effect of smoking, Casarett was of a similar opinion (14).

## SELENIUM

At present there is still no substantial evidence implicating selenium as a respiratory carcinogen, although this is still somewhat disputed (29, 100, 101).

## TOBACCO PESTICIDES AND GROWTH INHIBITORS

The most widely used sucker growth inhibitor is maleic hydrazide. This agent was recently reported to be carcinogenic (25). Tobacco leaf and cigarette smoke are known to contain organic pesticides (32, 104). The first identified carcinogenic pesticide in tobacco and cigarette smoke is 1,1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl) ethane (o,p'-DDD) (38, 56), which is a technical by-product of the commercial insecticide p,p'-DDD. At present there is no known evidence of chlorinated insecticides contributing to tobacco carcinogenesis.

## POSSIBLE FUNGAL CONTAMINATION OF TOBACCO

The mold *Aspergillus flavus* is known to synthesize the carcinogens of the aflatoxin group (17). However, a recent investigation reported

the absence of these agents in tobacco and cigarette smoke (90). Nevertheless, further studies are indicated to evaluate the possibility that some tobaccos may be contaminated with carcinogens produced by fungi.

## EXPERIMENTAL ASPECTS OF CARCINOGENESIS

### PASSIVE INHALATION OF TOBACCO SMOKE

In attempting to reproduce lung cancer in experimental animals, the limitations of presently available bioassays, mainly passive inhalation studies, have been discussed in the previous Reports (91, 92). Large scale studies in which a variety of animals have been exposed to the passive inhalation of tobacco smoke have essentially failed in producing squamous cell cancer of the lung (104).

The difficulties with passive inhalation studies in animals relate in part to the toxicity of carbon monoxide and nicotine. The defensive "filtration" capabilities of the nasal passages and the epithelium of the upper respiratory tract, necessitate relatively high exposure levels, which in the case of tobacco smoke cannot adequately be accomplished by passive inhalation methodologies.

Some laboratory studies failed to produce squamous cell cancer in C57 black mice even though some of the animals were previously inoculated with Swine influenza virus (106). Harris and Negrone (35), in experiments with C57 black mice, some of which were inoculated with viruses, achieved some enhancement of adenocarcinoma, but did not produce any proven squamous cell cancers.

Long-term cigarette smoke exposures in hamsters led only occasionally to tracheal papillomas and not to squamous cancer (20). However, one could sensitize these animals with diethylnitrosamine and enhance the tumor production initiated by this carcinogen by a variety of volatile irritants including tobacco smoke.

### ACTIVE INHALATION OF TOBACCO SMOKE

Active tobacco smoke inhalation studies as reported in the 1967 Report (92) have shown that hyperplastic and metaplastic changes can be produced in the lungs of dogs. These studies are expensive and it is difficult to keep the dogs alive long enough to permit the expected development of neoplastic transformation. Auerbach, et al. (4) in continuing experiments with "smoking" dogs, have shown all the bronchial epithelial changes including dysplasia, which is the most advanced stage of pre-malignant change. More research is needed to elucidate the biomechanisms involved in the pathogenesis of lung cancer caused by tobacco smoking.

## LUNG CANCER

### MORTALITY

The annual number of deaths in the United States from cancer of the lung (ICD Code 162, 163) increased from 18,313 deaths in 1950 to 48,483 in 1965 (95). During the same period of time the crude death rate rose from 12.2 deaths per 100,000 population to 25.0 deaths per 100,000 population. The lung cancer age-adjusted mortality rate for males increased from 18.5 per 100,000 population in 1950 to 39.2 per 100,000 population in 1965; while in the females, the age-adjusted rates increased from 3.9 to 6.4 per 100,000 population over the same period.

The age-specific death rates for males show an increase with age up to the 65 to 74 year age group, and then a decline. On the other hand, the female lung cancer death rates show a relatively steady increase with age, averaging approximately 7 additional deaths per 100,000 population between each ten year age group. As a result, the male to female mortality ratio varies from a low of 2.0 for the 25 to 34 year age group, to a high of 8.5 for the 65 to 74 year age group.

TABLE 1.—*Death rates per 100,000 population for lung cancer, by age and sex, 1965*

Sex	25-34 years	35-44 years	45-54 years	55-64 years	65-74 years	75-84 years	85 years and over
Males.....	1. 2	13. 2	58. 2	159. 2	269. 3	226. 4	152. 7
Females.....	0. 6	4. 4	13. 7	22. 1	31. 6	36. 5	45. 6
Ratio M/F.....	2. 0	3. 0	4. 2	7. 2	8. 5	6. 2	3. 3

SOURCE: National Center for Health Statistics (96).

### RETROSPECTIVE STUDIES

Studies in Iceland uniquely support the evidence that the increase in lung cancer is related to the increase in cigarette consumption. Iceland is a small country with a total population of about 200,000. There is relatively little air pollution, due mainly to the use of hot water springs instead of the combustion of fuel as a source of heating. Dungal (21) in 1950 noted a beginning rise in lung cancer in Iceland, associated with the rise in cigarette consumption during and after World War II. He predicted that if the cigarette consumption continued to rise, the 20 to 30 year lag in lung cancer death rates would begin to become apparent during the decade 1960-1970. Thorarinsson, et al. (87) reported a large increase in the lung cancer incidence in Iceland from 1931 to



1964, corresponding to a marked increase in per capita cigarette sales. The average annual incidence of lung cancer during the 10-year period, 1955-1964, was 12.1 in men and 6.5 in women per 100,000 population. However, comparing the first and second 5-year intervals, there was a 30 percent increase in lung cancer incidence in men and a 52 percent increase in women (table 2).

TABLE 2.—Average annual incidence rates for cancer of the lung, by sex: Iceland, 1955 to 1964

[Rate per 100,000 population]

Sex	1955-59	1960-64	1955-64
Males.....	10.3	13.6	12.1
Females.....	5.1	7.8	6.5

SOURCE: Thorarinsson, H. et al. (87).

Although the total number of deaths was small, 88 percent of the histologically classifiable tumors were of the squamous, undifferentiated, or oat-cell varieties. Ninety percent of the squamous, 82 percent of the oat-cell cancers, and 33 percent of the undifferentiated or adenocarcinomas occurred in smokers.

A small study by Guillian, et al. (31) again illustrates that cigarette smoking is also associated with adenocarcinoma of lung cancer. Of 24 cases of adenocarcinoma of the lung in men, a smoking history could be determined in 22 cases. Of these, 91 percent were smokers.

In a large retrospective study of 1,787 lung cancer patients in Japan by Ishikawa (42), adenocarcinoma was the most frequent histologic type noted in both males and females who did not smoke. Squamous cell carcinoma was the most frequent histologic type in male cigarette smokers and undifferentiated carcinoma the most frequent type in female cigarette smokers.

Of the male and female lung cancer patients, 22.6 and 2.9 percent, respectively, were smokers of over 30 cigarettes a day. Ishikawa compared this to the corresponding smoking habits of patients in a large ongoing prospective study of Hirayama (discussed later) which showed only 4.3 percent of the adult males over age 40 and 0.1 percent of the adult females over age 40 smoking 30 cigarettes a day or more.

Abelin, et al. (1) showed that the relative risk of lung cancer in Switzerland was associated with heavy cigar and pipe smoking (as well as cigarette smoking) to a much greater degree than previously reported. Most other studies have not shown a high association of lung cancer with cigar and pipe smoking. The authors suggest that their findings might be due to differences in either the amount smoked and/

or the carcinogenicity of Swiss and German cigars as compared to American cigars. The difference might also be explained by the greater use and more frequent inhalation of small cigars in Switzerland as compared to other countries where larger cigars are more commonly smoked but rarely inhaled.

### PROSPECTIVE STUDIES

The major, long-term, prospective studies were reviewed in the 1967 Report. The Doll and Hill (18, 19) study is still in progress, but no new data have become available. Data collection for the Best, Hammond, and Dorn studies (5, 34, 46) are completed, but various aspects are still being analyzed and new information will appear in the future.

Preliminary data from a large scale prospective study (37) of 265,118 men and women in Japan show that the death rate from lung cancer is significantly higher in cigarette smokers as compared to non-smokers for both males and females. There is also a positive correlation between lung cancer death rates and both the amount smoked and the

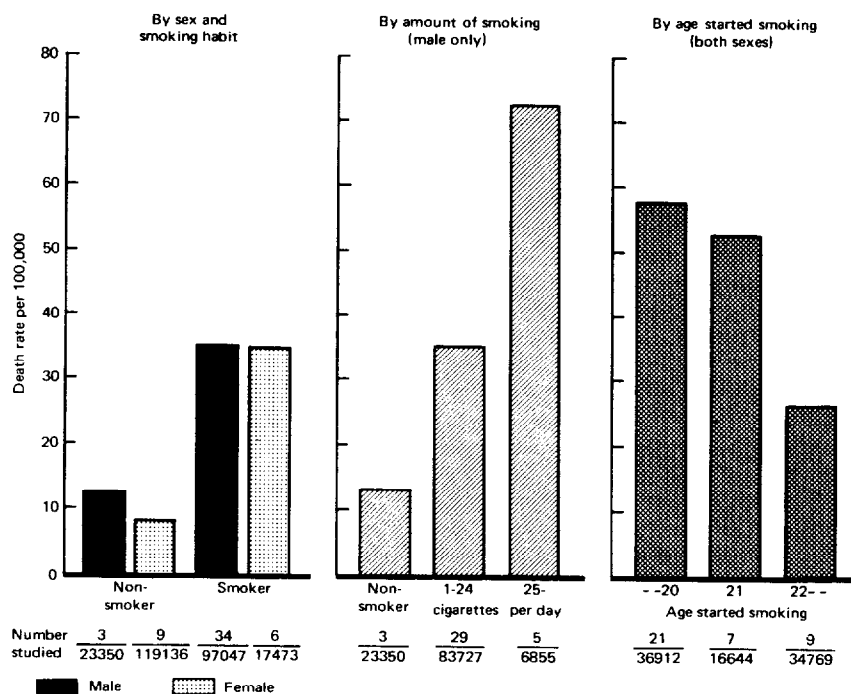


FIGURE 1—Death rates for lung cancer, among persons age over 40 years, classified by sex and extent of cigarette smoking, and by age smoking began: Study of 29 Health Center Districts in Japan, January 1966 to March 1967.

SOURCE: Hirayama, T. (37)

age smoking began, but the number of deaths is too small for adequate analysis at this time.

#### LUNG CANCER RELATIONSHIPS IN WOMEN

Critics have tried to throw doubt on the smoking-lung cancer relationship by saying that the lung cancer death rates for women have increased only slightly as compared to the greater relative increase in the number of women smokers.

It is true that the lung cancer death rates for women are presently much lower than the corresponding rates for men. Women presently account for only about one-sixth of the total deaths from lung cancer. But since 1930 the lung cancer death rate in women has increased over 400 percent. Over the past 14 years alone this increase has been over 50 percent (94). A most likely reason for the difference in male/female lung cancer death rates is that women still have not had the same degree of total exposure to cigarettes as have men. For instance, as late as 1955, only 24.5 percent of the adult female population (age 18 and over) were regular smokers compared to 52.6 percent of the adult male population (33). In 1966 the figures show only 33.6 percent of the adult females smoking (age 21 and over) as compared to 51.8 percent of the adult males. Also, the female smoker's per capita consumption was about 26 percent less than that of the male smoker in 1955, and about 20 percent less in 1966 (93). In addition, it has been shown that women smoke differently than men do (99). They do not smoke cigarettes as far to the end, where proportionally more nicotine and "tars" are inhaled than from the first part of the cigarette. Women smoke more filter-tip cigarettes than men, and smoke more "low tar and nicotine" cigarettes than do men. They also inhale less frequently and deeply than men. Furthermore, cigarette smoking still tends to be heavily concentrated in those women under the age of 50 years, prior to the age at which lung cancer is mostly likely to occur.

An analysis of the lung cancer death rates (94) shows that, "Until 1960 the ratio of the death rate in the male population for this cause to the corresponding death rate in the female population continued upward. But after 1960 this ratio leveled off, reflecting the greater relative rise in mortality from lung cancer in the female population."

#### ADDITIONAL CONSIDERATIONS AND CONCLUSIONS

Filter cigarettes, in general, have lower "tar" and nicotine values than comparable non-filter cigarettes. In this respect, a study by Bross (9), shows preliminary evidence that smokers who switched to filter cigarettes have a decreased risk of developing lung cancer.

Graham (30) studied the smoking habits of male lung cancer patients and controls. Previously he showed, on smoking machines, that dif-

ferent patterns of cigarette smoking gave different "tar" yields. His lung cancer patients had significantly greater high "tar" yield cigarette smoking patterns than the controls. The risk of lung cancer increased with increase in: (1) the mean number of puffs per cigarette, (2) the average length of time taken to smoke a cigarette (except in the highest number of puffs category) and (3) taking more puffs towards the end of the cigarette. These findings add further support to the dose-response relationship between lung cancer and cigarette "tar" exposure.

As pointed out in the 1964 and 1967 Reports, there appear to be several other factors which may also contribute to the etiology of lung cancer, especially in the presence of cigarette smoking. However, there has been no evidence to refute the statement in the 1964 Report that, "Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction."

Of particular interest are the studies of Buell, et al. (11, 12). They reviewed various prospective and retrospective studies which showed that the urban-rural differences in lung cancer death rates in non-smokers were of the range of 2:1 to 4.4:1. However, the much greater effect of smoking on increasing the lung cancer death rates was evident by their statement "that smoking can act independently of the urban factor, the gradients among rural dwellers rising to as much as 10 to 15 fold for heavy smokers." With regard to the high levels of photochemical air pollutants in Los Angeles, they concluded: "With controls for cigarette smoking and length of residence, the risk of pulmonary cancer in Los Angeles, where photochemical air pollution levels are highest, was not greater than in other major metropolitan areas of California."

Although photochemical air pollution might not be a contributing factor to lung cancer mortality in man, as is the "sulfur dioxide" air pollution found in most industrial areas, it may be too early to ascertain any effects, since air pollution in Los Angeles only became a problem between 1945 and 1950.

Stocks (84, 85) shows that per capita solid fuel consumption has a positive correlation with lung cancer death rates but to a much lesser degree than per capita cigarette consumption. He suggests, therefore, that air pollution from solid fuel combustion is related to lung cancer death rates and that this might possibly be independent of cigarette smoking. However, Stocks did not determine the specific smoking histories of individuals who died from lung cancer.

Concurrent studies of cigarette smoking and air pollution, in the same populations with precise smoking histories on individuals who have died from lung cancer, might serve to clarify the probable interaction between cigarette smoking and air pollution or possible inde-

pendence of cigarette smoking from air pollution as they relate to the etiology of lung cancer.

The preponderance of evidence [1964 Report (91), 1967 Report (92), and this report] continues to indicate that most lung cancers occur in cigarette smokers and that cigarette smoking is the major cause of lung cancer. A majority of lung cancer cases are of the squamous cell variety and most investigators are in agreement that squamous cell carcinoma is rare in the male nonsmoker (3, 15, 103). The elimination of cigarette smoking would in time eliminate most lung cancer. That this is a real goal is supported by the study of British physicians (18, 19) reviewed in the 1967 report.

It is not disputed that some cases of lung cancer can occur in those people who have never smoked cigarettes or inhaled any form of tobacco smoke. In these cases air pollution possibly plays a larger role in the causation, but in most cases, it appears that it is the cigarette smoker who is especially susceptible to whatever additional risk for lung cancer may be presented by certain types of air pollution or other factors such as asbestos or uranium dust inhalation.

#### CANCER OF THE ORAL CAVITY

The 1967 report showed that the overall death rates for oral cancer remained about the same during the period 1950–1964. This was influenced somewhat by recent changes in the ICD Code.

It is interesting to note that the incidence rates of oral cancer have also remained relatively constant over the period 1935–1962,\* in spite of increased cigarette smoking (24). This may be explained, in part, by the fact that the numerators of such rates often include neoplasms coded to the International Classification of Disease, rubrics 140 through 148. These rubrics identify many oral and pharyngeal diagnostic sites which do not contribute equally to either the morbidity or mortality experience resulting from the use of tobacco. For example, preliminary findings in an unpublished study by Keller (47) suggest that salivary cancers (ICD rubric 142), unlike tongue and floor of mouth cancers, are not associated with the tobacco habit. The fact that pipe and cigar smoking in this country began to be replaced by cigarette smoking among men born subsequent to 1900 may also be significant, although this trend has leveled off and may even have been reversed since the health consequences of smoking cigarettes first came to public attention in the mid-1950's. In the population which accounts

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\*There is no national data collection on incidence rates of diseases. Several states have cancer registries which have information on the incidence of cancer in that particular state. The data from Connecticut are generally thought to reflect the changing patterns of cancer incidence throughout the United States. It is realized that there might be individual state differences. References to incidence rates in this chapter section are taken from the Connecticut data unless otherwise specified.

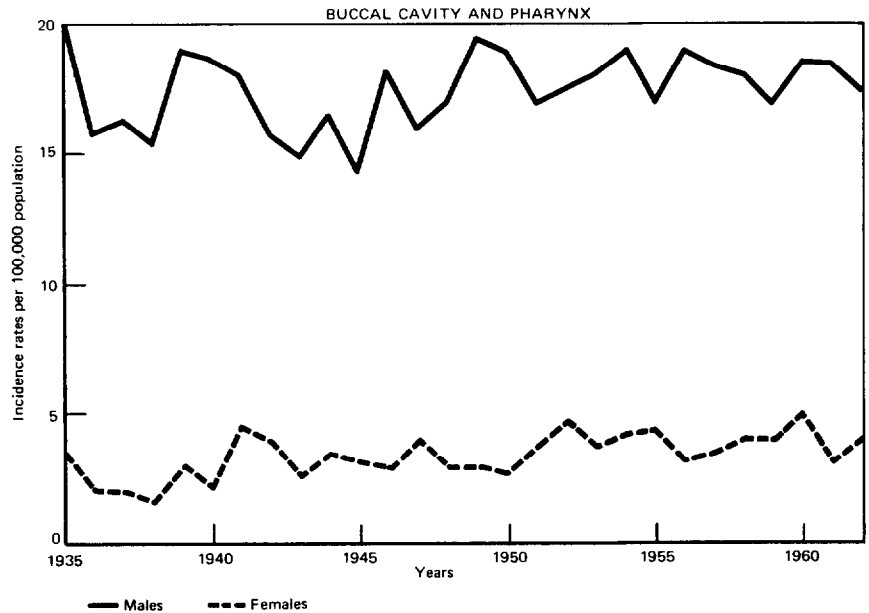


FIGURE 2—Age-adjusted rates of the incidence of cancer of the buccal cavity and pharynx, for males and females: Connecticut, 1935-1962.

SOURCE: Eisenberg, et al. (24).

for the bulk of oral cancer cases—men over 45—there has been a greater change in the form in which tobacco is used than in the proportion of men using tobacco.

Since pipe and cigar smoking is associated with oral cancer, with mortality ratios not very different from those for cigarette smokers, the constant incidence rates may reflect the fact that the proportion of tobacco users among men over 45 has been fairly stable.

A review of the recent retrospective studies shows a relationship of oral cancer to all forms of the tobacco habit (22, 26, 53, 54, 77, 78, 79, 98). This includes the use, in the mucobuccal fold, of either snuff, among women (10, 22, 71, 72, 81), or the betel nut quid with tobacco, among the residents of India and Southeast Asia (36, 54, 77, 78, 79, 98).

Reddy has produced tumors in mice by daily instillation of a "pan" mixture with tobacco (the same mixture used for chewing) into the vaginas of virgin mice (69).

There is evidence that in the presence of tobacco consumption, alcohol may also be a factor in the etiology of oral cancer (48, 49, 50, 97). In a recent study on male veterans, Keller concluded, "\* \* \* heavy smoking, heavy drinking and liver cirrhosis (either alone or as a measure of heavy drinking) are associated with cancer of the

mouth and pharynx" (48). Since most people who drink large amounts of alcohol regularly are also heavy users of tobacco, it is difficult to identify the relative contribution of these two factors or the role of the nutritional problems often associated with heavy alcohol use.

Additional data have been reported by Moore (62), on patients developing second primary mouth and throat cancers, after having been cured for at least three years prior to development of the cancer. These patients were all asymptomatic for at least three years prior to development of the second cancer. Of 117 patients with adequate smoking histories only 4 of 43 (9 percent) who quit smoking after the first cancer, developed a new primary. On the other hand, 27 of 74 patients (36 percent) who continued to smoke developed a second primary cancer. These data support the important contribution of smoking to the etiology of mouth and throat cancer.

Roth, et al. (73, 74) recently have shown that the dye-binding capacity of DNA of oral epithelial cells is significantly enhanced in cigarette smokers in contrast to nonsmokers, probably reflecting an increase in the DNA content of oral epithelial cells in smokers. This suggests some alteration in the DNA which may be a factor in oral carcinogenesis. Smokers had values of dye-binding capacity intermediate between nonsmokers and 21 patients with proven oral cancer. Those smokers who refrained from smoking for up to nine months showed a significant decrease towards more normal values.

It is clear that people who use tobacco have higher rates of oral cancer than those who do not. Research is needed to identify the dose relationships, to determine whether or not there are dosage thresholds, and to clarify the relationships between dosage, style of tobacco use, and part of the mouth affected.

It seems likely that factors such as alcohol consumption, nutritional problems, and oral hygiene may be interrelated with the tobacco habit in a fairly complex pattern. More research is needed to clarify these relationships.

For patients with oral cancer, and probably for those at a high risk of oral cancer because of other exposures, cessation of tobacco use can make an important contribution to reducing the risk of a new primary cancer.

### CANCER OF THE LARYNX

Cancer of the larynx is mainly a disease of male smokers. Of the 2,629 deaths in 1965, over 88 percent were men. The 1967 report noted that the death rate for cancer of the larynx had not increased significantly since 1950. The incidence rates, however, have shown a steady increase since 1935.

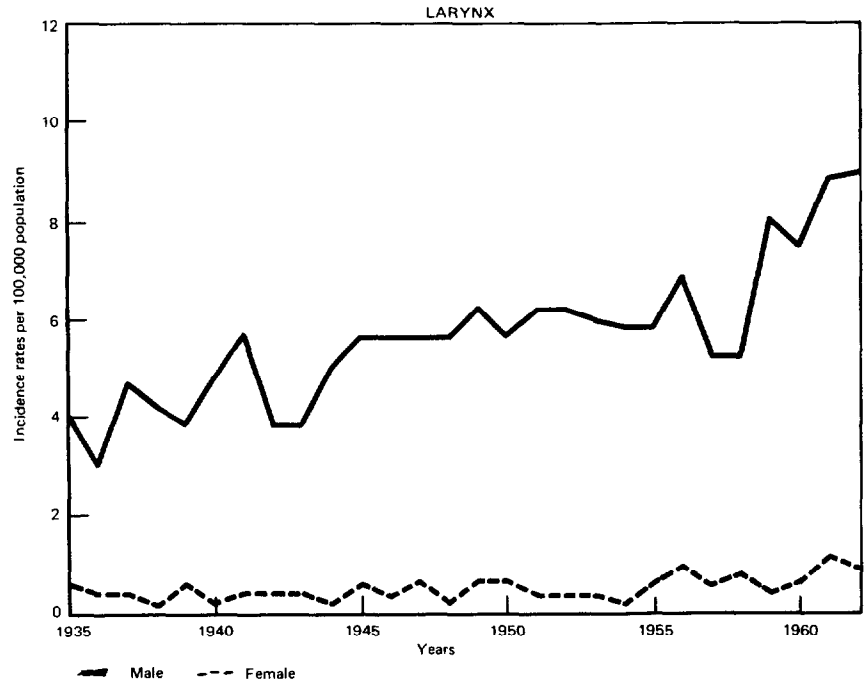


FIGURE 3—Age-adjusted rates of the incidence of cancer of the larynx, for males and females: Connecticut, 1935-1962  
SOURCE: Eisenberg et al. (24).

The American Cancer Society (2) estimates the occurrence of 6,000 new cases of cancer of the larynx in 1968 but only about 2,800 deaths, due to relative curability of this disease if diagnosed early.

Several retrospective studies have again shown the extremely high rate of smokers [98 percent (86), 92 percent (75)] among patients with cancer of the larynx.

### CANCER OF THE ESOPHAGUS

As reported in the 1967 Report (92) the death rates for cancer of the esophagus have increased only slightly in the period 1950-1964. The large scale prospective studies (18, 19, 34, 46) showed mortality ratios up to 11 in heavy cigarette smokers, while pipe and/or cigar smokers had ratios up to 5.

Preliminary data from a prospective study (37) in Japan also indicate an increased frequency of death from cancer of the esophagus among smokers as compared to nonsmokers.

No further information has become available on the relationship of esophageal cancer to alcohol and/or other confounding variables as discussed in the 1967 report.



## CANCER OF THE PANCREAS

The 1967 report implied a relationship between smoking and pancreatic cancer due to the somewhat higher mortality ratios observed in three of the large scale prospective epidemiologic studies.

The American Cancer Society estimates that deaths due to cancer of the pancreas will total 18,000 in 1968 with a male/female ratio of approximately 3:2. The overall death rate for cancer of the pancreas has shown a steady rise; from 7.2 to 8.4 in males (+17 percent) and 4.4 to 4.9 (+11 percent) in females, for the time period 1953-55 to 1963-65 (2). The incidence rates have increased almost 50 percent in males since 1935, with no apparent increase for females.

In the past year, preliminary evidence from two retrospective studies (43, 102) has shown that only 10 percent of the patients with cancer of the pancreas are nonsmokers. The risk of developing cancer of the pancreas appears to increase in proportion to the amount smoked.

Preliminary data from a prospective study (37) in Japan also shows a significantly higher frequency of deaths from pancreatic cancer among smokers as compared to nonsmokers.

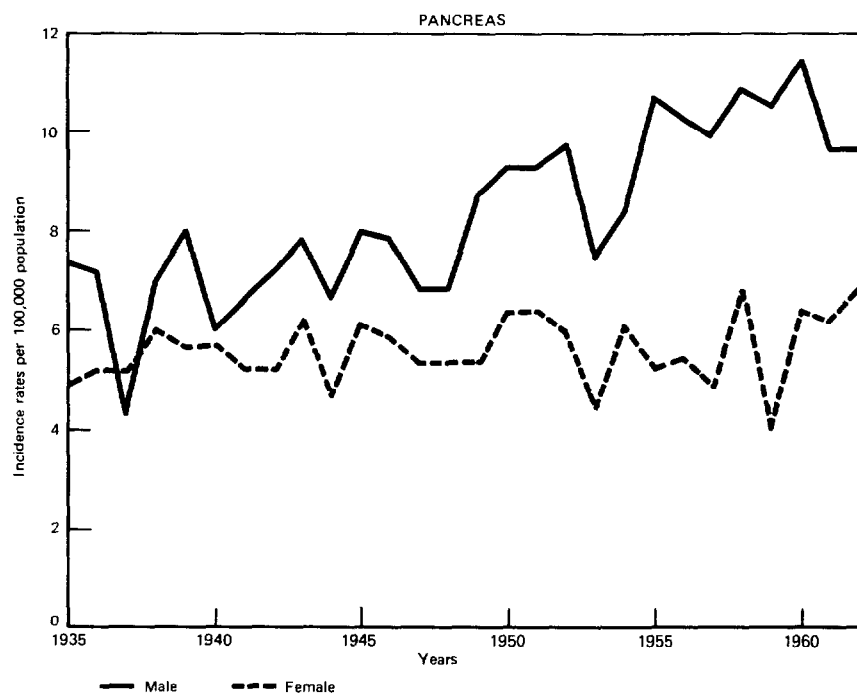


FIGURE 4—Age-adjusted rates of the incidence of cancer of the pancreas, for males and females: Connecticut, 1935-1962.

SOURCE: Eisenberg, et al. (24).

These studies strengthen the earlier indications of an association between smoking and pancreatic cancer, but further research is needed in this area to elucidate the significance of this association.

## GENITO-URINARY CANCER

### CANCER OF THE BLADDER

As stated in the 1967 Report, there has been no increase in male or female death rates for cancer of the bladder over the 15 year period 1950–1964. However, the incidence rates for males have increased over 75 percent in the 25-year period from 1935–37 to 1960–62, and about 26 percent in the 15 year period from 1945–47 to 1960–62.

Deeley, et al. (16) reported on a retrospective study of 127 patients with cancer of the bladder and 126 patients with lung cancer, all matched with controls. The smoking “factors” (amount times duration of smoking) were significantly greater among cases than controls for both cancer sites. Even by age-groups, the “mean smoking factor” for either cancer was higher for cases than for controls. Preliminary data

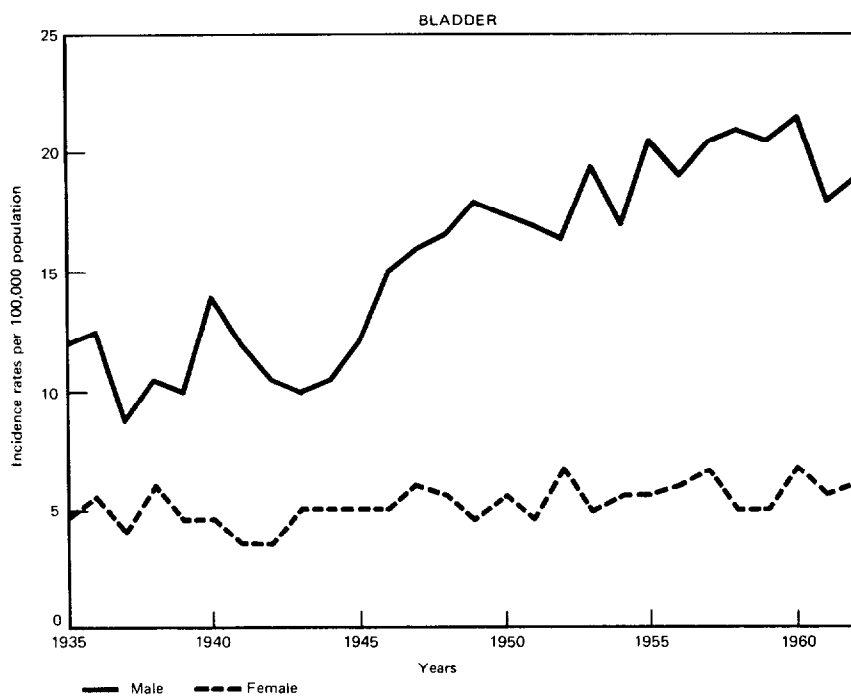


FIGURE 5—Age-adjusted rates of the incidence of cancer of the bladder, for males and females: Connecticut, 1935–1962.

SOURCE: Eisenberg, et al. (24)

from a prospective study (37) in Japan shows a higher frequency of deaths from bladder cancer among smokers.

Certain amino acids, as found in tobacco, form trace amounts of alpha- and beta-naphthylamines upon pyrolysis (59). The latter agent is an established bladder carcinogen. So far, however, only its isomeric alpha-naphthylamines has been identified in cigarette smoke (60, 67).

Further investigation is needed on the carcinogenic metabolites of tryptophan which have been shown to be increased in the urine of cigarette smokers (92).

### CANCER OF THE KIDNEY

The 1967 Report did not mention the association between smoking and cancer of the kidney.

The U.S. Veterans study (46) shows increasing mortality ratios for cancer of the kidney with the amount of cigarette smoking. There is no apparent relationship with pipe and/or cigar smoking.

TABLE 3.—Mortality ratios and death rates for cancer of the kidney in U.S. veterans, by age, type and amount smoked for current smokers only

	Number of cigarettes smoked per day					Pipe and/or cigars	Cigars	Pipe
	0	1-9	10-20	21-39	40 and over			
Mortality ratios.....	1. 00	. 97	1. 34	1. 68	2. 75	1. 15	. 77	1. 32
Death rates:								
Age 45-54.....								
Age 55-64.....	8	5	8	10	26	5	7	2
Age 65-74.....	14	7	15	27	13	14	2	25
Age 75-84.....	7					40		

SOURCE: Kahn, H. A. (46).

TABLE 4.—Mortality ratios and death rates for cancer of the kidney in male cigarette smokers, by specified age groups

	Cigarette smokers	
	Age 45-64	Age 65-79
Mortality ratios.....	1. 42	1. 57
Death rates.....	<sup>1</sup> (4)6	<sup>1</sup> (15)23

<sup>1</sup> Numbers in parentheses indicate death rates for persons who have never smoked regularly.

SOURCE: Hammond, E. C. (34).

Hammond (34) has also demonstrated higher mortality ratios in cigarette smokers for cancer of the kidney.

Preliminary evidence from a retrospective study in progress (102) suggests that cigarette smokers, especially those who smoke over 35 cigarettes a day, are over-represented in those patients with cancer of the kidney. More research should be done to try to ascertain if there is a meaningful relationship between smoking and cancer of the kidney.

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