The Health Consequences of SMOKING

1968 SUPPLEMENT TO THE

1967 Public Health Service Review

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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.

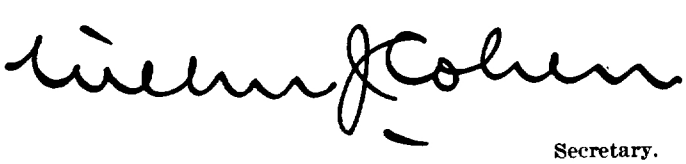
I therefore recommend:

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.

* 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 biomechanism 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.

William H. Stewart

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

Current Information on the Health Consequences of Smoking

Highlights of The Report

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

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
U.S. VETERANS: MEN					
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 [1]	1. 83	2. 76	1. 72	1. 67	1. 36
Difference in death rates per 100,000 [2]	105	464	763	1, 621	2, 257
Excess deaths as percentage of total [3]	33	43	21	17	8
HAMMOND MEN					
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 [1]	1. 89	2. 28	1. 83	1. 51	1. 23
Difference in death rates per 100,000 [2]	187	519	1, 000	1, 620	1, 811
Excess deaths as percentage of total [3]	33	38	25	13	4
HAMMOND WOMEN					
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 [1]	1. 13	1. 26	1. 20	1. 17	. 99
Difference in death rates per 100,000 [2]	21	80	104	316	68
Excess deaths as percentage of total [3]	5	9	4	2	------

[1] Mortality ratios—death rate for current cigarette smokers divided by death rate for those who never smoked regularly.

[2] Differences in death rates—death rate for current cigarette smokers minus death rate for those who never smoked regularly.

[3] 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 nonsmoking 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).

REFERENCES

(*1*) HAMMOND, E. C. Life expectancy of American men in relation to their smoking habits. Presented at the World Conference on Smoking and Health, New York City, September 11–13, 1967. 23 pp.

(*2*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Public Health Service Review: 1967. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1967. 227 pp.

(*3*) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.

PART II

Technical Reports on the Relationship of Smoking to Specific Disease Categories

CHAPTER 1

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.

*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 followup 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 that 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

* Also may include mortality data in this presentation.

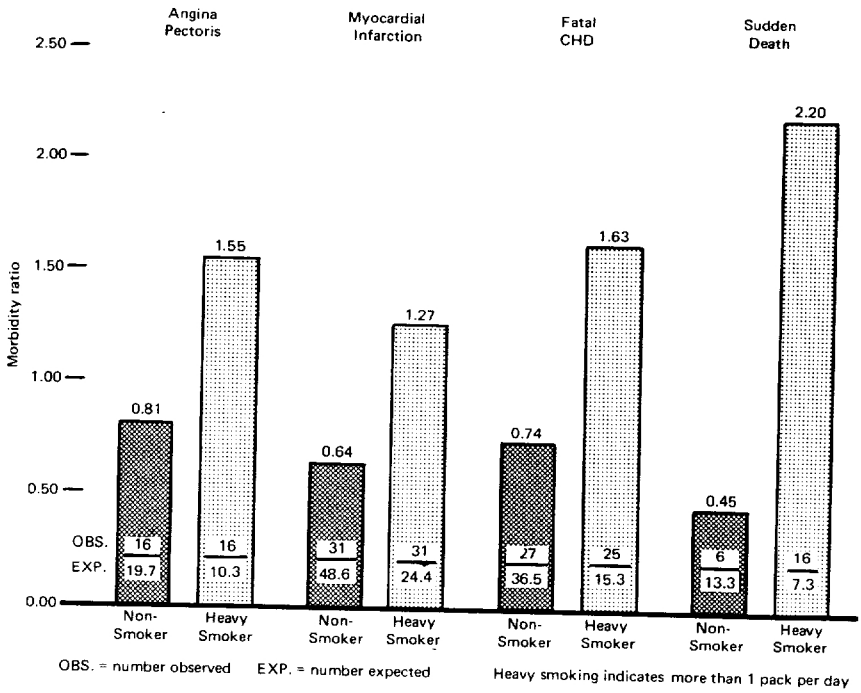


FIGURE 1—Morbidity ratios for specified manifestations of coronary heart disease, among men aged 30–59 years at entry into Framingham Heart Study, classified by smoking habit: 12 years' experience.

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.

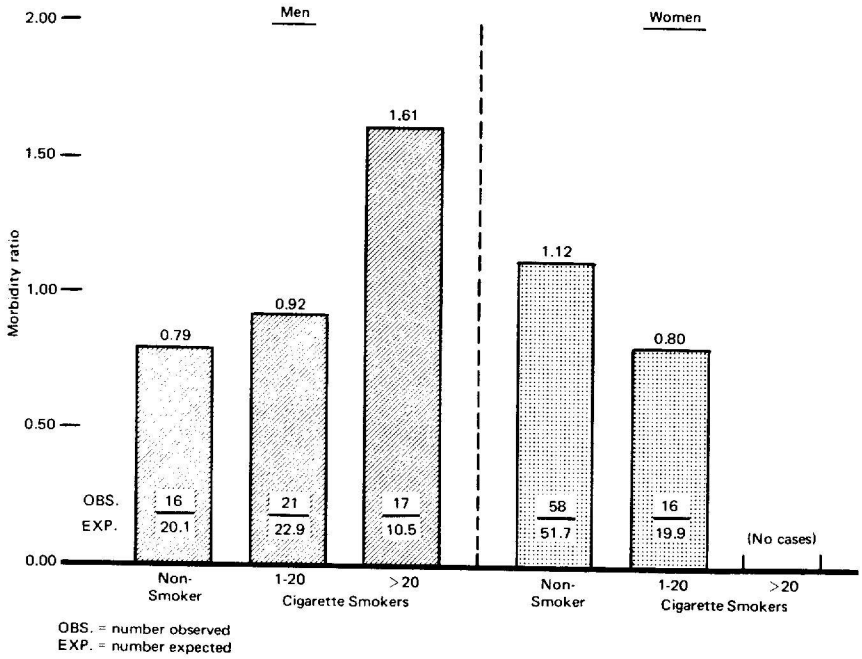


FIGURE 2—Angina pectoris morbidity ratios among persons aged 30–59 years at entry into Framingham Heart Study, classified by sex and number of cigarettes smoked: 12 years' experience.

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 transit 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.

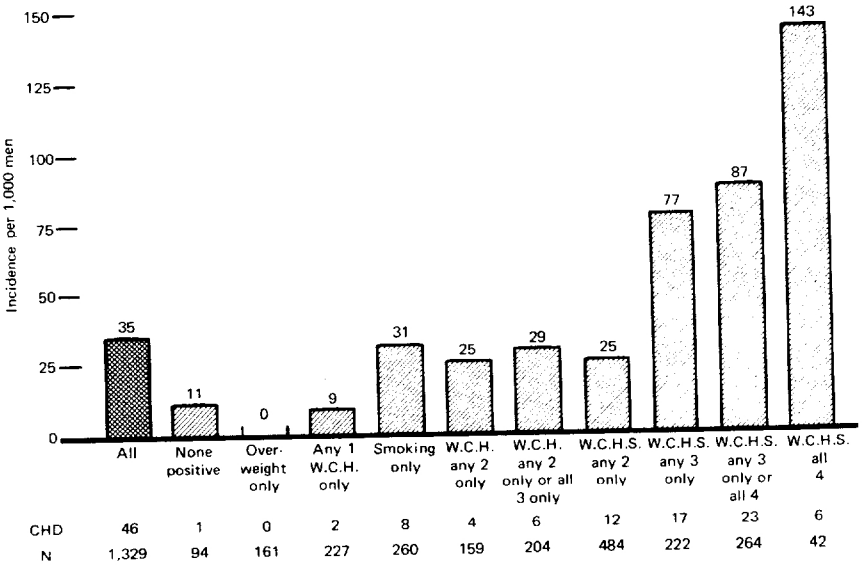
Mulcahy (*107*), in a retrospective study of 100 women coronary heart disease patients under 60 years of age, reported that 50 to 60 percent had diastolic hypertension (>90 mm. Hg.). Hypertension and cigarette smoking, together or separately, were present in over 80 percent of these patients.

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.[1]

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

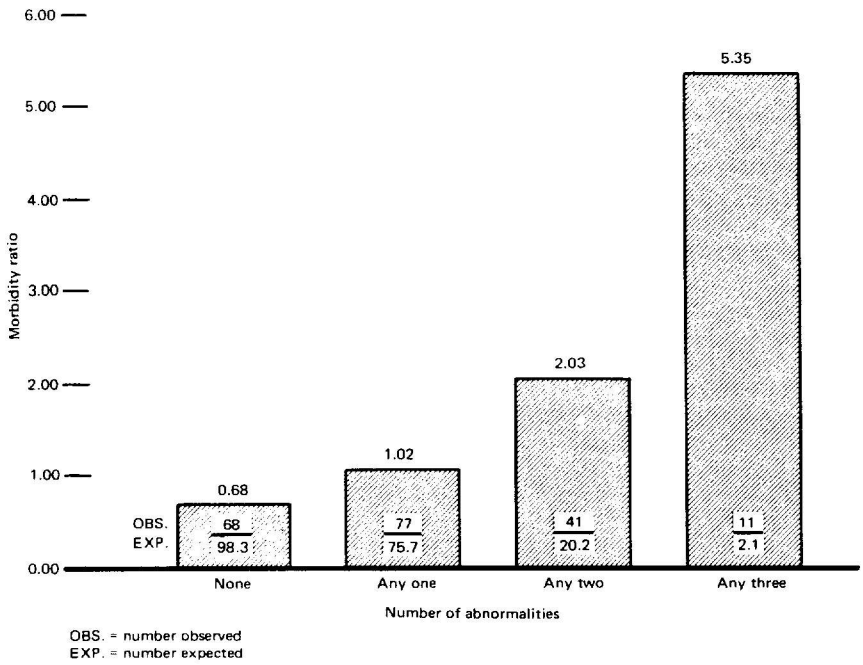


FIGURE 4—Myocardial infarction morbidity ratios among men aged 30–59 years at entry into Framingham Heart Study, classified according to presence of selected risk factors: 12 years experience (Risk factors are: cholesterol level over 250 mg/100 ml., systolic blood pressure over 160 mm. Hg., smoking over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

So rce: Weinblatt, E. (*155*).

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 nonsmokers: 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 trigylceride 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 μg./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.

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 μg./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 activiation by nicotine could lead to increased total peripheral resistance with impaired storke 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 μg./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. Weissler, 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. Kershbaum, 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, nonesterified 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 corticosteriod levels in smokers. Whether the "hyperinsulinism" reported to be present in smokers is related to increased adrenal corticosteriods 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.

CITED REFERENCES

(*1*) ARDLIE, N. G., GLEW, G., SCHWARTZ, C. J. Influence of catecholamines on nucleotide-induced platelet aggregation. Nature (London) 212 (5060) : 415–417, October 22, 1966.

(*2*) ASTRUP, P., KJELDSEN, K., WANSTRUP, J. Enhancing influence of carbon monoxide on the development of atheromatosis in cholesterol-fed rabbits. Journal of Atherosclerosis Research 7 : 343–354, 1967.

(*3*) AUERBACH, O., HAMMOND, E. C., GARFINKEL, L. Thickening of walls of arterioles and small arteries in relation to age and smoking habits. New England Journal of Medicine 278(18) : 980–984, May 2, 1968.

(*4*) AYRES, S. M. Personal communication. March 1968.

(*5*) BAER, D. J. Height, weight, and ponderal index of college male smokers and nonsmokers. Journal of Psychology 64 : 101–105, September 1966.

(*6*) BELLET, S., KERSHBAUM, A., MEADE, R. H., JR., SCHWARTZ, L. The effect of tobacco smoke and nicotine on the normal heart and in the presence of myocardial damage produced by coronary ligation. American Journal of the Medical Sciences 201(1) : 40–51, January 1941.

(*7*) BERGEL, D. H., MAKIN, G. S. Central and peripheral cardiovascular changes following chemical stimulation of the surface of the dog's heart. Cardiovascular Research 1(1) : 80–90, 1967.

(*8*) BESTERMAN, E., MYAT, G., TRAVADI, V. Diurnal variations of platelet stickiness compared with effects produced by adrenaline. British Medical Journal 1 : 597–600, March 11, 1967.

(*9*) BIRNSTINGL, M., COLE, P., HAWKINS, L. Variations in oxyhaemoglobin dissociation with age, smoking and Buerger's Disease. British Journal of Surgery 54(7) : 615–619, July 1967.

(*10*) BLACKBURN, H., KEYS, A., KARVONEN, M., VAN BUCHEM, F. S. P., TAYLOR, H. L. Relation of "positive" postexercise electrocardiographic responses to other characteristics of risk. Circulation 36(4) (Supplement II) : 70, October 1967.

(*11*) BLOMSTRAND, R., LUNDMAN, T. Serum lipids, smoking and heredity. Acta Medica Scandinavica (Supplement 455) : 51–60, 1966.

(*12*) BRACHFELD, N., KUEHN, P., KAWADE, M., ORAN, E. Nicotine medicated release of myocardial cell and lysosomal enzymes. Annals of Internal Medicine 66(5) : 1034, May 1967.

(*13*) BRAUNWALD, E., CHIDSEY, C. A., HARRISON, D. C., GAFFNEY, T. E., KAHLER, R. L. Studies on the function of the adrenergic nerve endings in the heart. Circulation 28(5) : 958–969, November 1963.

(*14*) BRAY, C., MCDONALD, L. A new platelet defect in patients with ischaemic heart disease. British Heart Journal 28(3) : 429, May 1966.

(*15*) BURCH, G. E., DEPASQUALE, N. P. The hematocrit in patients with myocardial infarction. Journal of the American Medical Association 180(1) : 63–70, April 7, 1962.

(16) BURCH, G. E., DEPASQUALE, N. P. Hematocrit, viscosity and coronary blood flow. Diseases of the Chest 48(3): 225–232, September 1965.

(17) BURCH, G. E., DEPASQUALE, N. P. Sudden, unexpected, natural death. American Journal of the Medical Sciences 249: 86–97, January 1965.

(18) CEDERLOF, R. The value of twin studies in epidemiology. World Medical Journal 14(6): 168–171, November–December 1967.

(19) CEDERLOF, R., FRIBERG, L., JONSSON, E., KAIJ, L. Morbidity among monozygotic twins. Archives of Environmental Health 19(2): 346–450, February 1965.

(20) CEDERLOF, R., FRIBERG, L., JONSSON, E., KAIJ, L. Respiratory symptoms and "angina pectoris" in twins with reference to smoking habits. Archives of Environmental Health 13(6): 726–737, December 1966.

(21) CHIDSEY, C. A., BRAUNWALD, E., MORROW, A. G. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. American Journal of Medicine 39(3): 442–451, September 1965.

(22) CHIDSEY, C. A., SONNENBLICK, E. H., MORROW, A. G., BRAUNWALD, E. Norepinephrine stores and contractile force of papillary muscle from the failing human heart. Circulation 33(1): 43–51, January 1966.

(23) CLARK, V. A., CHAPMAN, J. M., COULSON, A. H. Effects of various factors on systolic and diastolic blood pressure in the Los Angeles Heart Study. Journal of Chronic Diseases 20: 571–581, 1967.

(24) COHEN, A. M., SHAFRIR, E. Carbohydrate metabolism in myocardial infarction. Behavior of blood glucose and free fatty acids after glucose loading. Diabetes 14(2): 84–86, February 1965.

(25) COLEMAN, H. N., SONNENBLICK, E. H., BRAUNWALD, E. Mechanism of the norepinephrine-induced stimulation of myocardial oxygen consumption as studied in the isolated cat papillary muscle. Circulation (Supplement II) 36(4): 89, October 1967.

(26) CONNOR, W. E., HOAK, J. C., WARNER, E. D. Fatty acids and thrombus formation. In: Sasahara, A. A., editor. Pulmonary Embolic Disease. London, 1965. Pp. 50–58.

(27) CORSINI, G. C., PURI, P. S., BING, R. J. Effect of nicotine on capillary flow and vascular bed of the heart in presence and absence of experimental coronary artery insufficiency. Federation Proceedings 27(2): 632, March–April 1968.

(28) CZOCHRA-LYSANOWICZ, Z., GORSKI, M., KEDRA, M. Wplyw nikotyny i kofeiny na rozwoj miazdzycy u krolikow. Annales Universitatis Mariae Curie-Sklodowska: Section D: Medicina 14(20): 181–206, 1959.

(29) DÖRKEN, H. The etiology of myocardial infarction—with special reference to cigarette smoking among young coronary patients and those with second heart attacks. In: Wynder, E. L., Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press)

(30) DÖRKEN, H. Die Rauchgewohnheiten bei Jungeren Frauen mit Herzinfarkt. Münchener Medizinische Wochenschrift 109(41): 2129–2134, January 1967.

(31) DÖRKEN, H. Die Rauchgewohnheiten bei Jungeren Herzinfarkt-Patienten. Münchener Medizinische Wochenschrift 109(4): 187–192, January 27, 1967.

(32) EDMUNDOWICZ, A. C., CIPOLLONI, P. B., PENROD, K. E. Cardiovascular responses to cigarette smoke and nicotine in dogs following beta-adrenergic blockade with propranolol. (Abstract) Federation Proceedings 24: 713, March–April 1965.

(33) ELIOT, R. S., BRATT, G. S. Personal communication, April 1968.

(34) ELIOT, R. S., MIZUKAMI, H. Oxygen affinity of hemoglobin in persons with acute myocardial infarction and in smokers. Circulation 34: 331–336, August 1966.

(35) ELLIOTT, W. C., GORLIN, R. The coronary circulation, myocardial ischemia, and angina pectoris. Modern Concepts of Cardiovascular Disease 35(10): 111–116, October 1966.

(36) Epidemiological studies related to coronary heart disease: Characteristics of men aged 40–59 in seven countries. F. Smoking habits. Acta Medica Scandinavica (Supplement 460): 304–315, 1967.

(37) EPSTEIN, F. H. Hyperglycemia. A risk factor in coronary heart disease. Circulation 36: 609–619, October 1967.

(38) EPSTEIN, F. H. Predicting coronary heart disease. Journal of the American Medical Association 201(11): 795–800, September 11, 1967.

(39) EPSTEIN, F. H. Some uses of prospective observations in the Tecumseh Community Health Study. Proceedings of the Royal Society of Medicine 60(1): 4–8, January 1967.

(40) FIDANZA, F., IMBIMBO, B., DI BENEDETTA, C. Indagine epidemiologica delle cardiopatie ischemiche nei reclusi del penitenziario di S. Stefano di Ventotene. Giornale dell'-Arteriosclerosi 4: 255–267, 1966.

(41) FRANKL, W. S., FRIEDMAN, R., SOLOFF, L. A. Cardiac output, blood pressure and free fatty acid responses to smoking in the nonbasal state. American Journal of the Medical Sciences 252(1): 39–44, July 1966.

(42) FRANKL, W. S., SOLOFF, L. A. The hemodynamic effects of propranolol hydrochloride after smoking. American Journal of the Medical Sciences 254(5): 623–628, November 1967.

(43) FRANKL, W. S., WINTERS, W. L., SOLOFF, L. A. The effects of smoking on the cardiac output at rest and during exercise in patients with healed myocardial infarction. Circulation 31(1): 42–44, January 1965.

(44) FRIEDEMANN, M., STEIM, H., EMMRICH, J., REINDELL, H. Der Herzinfarkt in Atiologiscer und katamnestischer Sicht. Deutsches Archiv fur Klinische Medizin 211: 261–296, 1965.

(45) FRIEDMAN, E. H., HELLERSTEIN, H. K. Occupational stress, law school hirearchy, and coronary artery disease in Cleveland attorneys. Psychosomatic Medicine 30(1): 72–86, January–February 1968.

(46) FRIEDMAN, G. D. Cigarette smoking and geographic variation in coronary heart disease mortality in the United States. Journal of Chronic Diseases 20: 769–779, 1967.

(47) GAZES, P. C., RICHARDSON, J. A., WOODS, E. F. Plasma catecholamine concentrations in myocardial infarction and angina pectoris. Circulation 19(5): 657–661, May 1959.

(48) GLYNN, M. F., MUSTARD, J. F., BUCHANAN, M. R., MURPHY, E. A. Cigarette smoking and platelet aggregation. Canadian Medical Association Journal 95: 549–553, September 10, 1966.

(49) GRAHAM, T. P., JR., COVELL, J. W., SONNENBLICK, E. H., ROSS, J., JR., BRAUNWALD, E. Control of myocardial oxygen consumption: Relative influence of contractile state and tension development. Journal of Clinical Investigation 47: 375–385, 1968.

(50) GREENSPAN, K., KNOEBEL, S. B., FISCH, C. Effects of nicotine upon human and canine cardiac action potential and contractile state. (Abstract) The Project for Research on Tobacco and Health 1964–1968. American Medical Association Education and Research Foundation. June 1968. Pp. 24–25.

(51) GROSGOGEAT, Y., ANGUERA, G., LELLOUCH, J., JACOTOT, B., BEAUMONT, J. L., PATOIS, E., MANIER, E. L'intoxication chronique par la nicotine chez

le lapin nourri au cholesterol. Effets sur la paroi aortique et sur la lipidemie. Journal of Atherosclerosis Research 5(3) : 291–301, 1965.

(52) GUDBJARNASON, S. Effect of nicotine administration on cholesterol metabolism of liver, serum, heart and brain. Journal of Pharmacology and Experimental Therapeutics 161(1) : 47–54, May 1968.

(53) GUTENKAUF, J. J., BRATT, G. T., ELIOT, R. S. Effect of cigarette smoking on the hemoglobin-oxygen dissociation curve. Circulation (Supplement II) 36(4) : 129, October 1967.

(54) HAMMOND, E. C. Smoking in relation to the death rates of 1 million men and women. In: Haenszel, W., editor. Epidemiological Approaches to the Study of Cancer and Other Diseases. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966. Pp. 127–204.

(55) HAMPTON, J. R., MITCHELL, J. R. A. Effect of aggregating agents on the electrophoretic mobility of human platelets. British Medical Journal 1: 1074–1077, 1966.

(56) HARLIN, W. R., OBERMAN, A., MITCHELL, R. E., GRAYBIEL, A. Constitutional and environmental factors related to serum lipid and lipoprotein levels. Annals of Internal Medicine 66(3) : 540–555, March 1967.

(57) HARRISON, M. J. G., MITCHELL, J. R. A. The influence of red blood cells on platelet adhesiveness. Lancet 2: 1163–1164, November 26, 1966.

(58) HASLAM, R. J. Role of adenosine diphosphate in the aggregation of human blood-platelets by thrombin and by fatty acids. Nature (London) 202: 765, 1964.

(59) HASS, G. M., LANDERHOLM, W., HEMMENS, A. Production of calcific athero-arteriosclerosis and thromboarteritis with nicotine, vitamin D, and dietary cholesterol. American Journal of Pathology 49(4) : 739–771, October 1966.

(60) HERMAN, M. V., ELLIOTT, W. C., GORLIN, R. An electrocardiographic, anatomic, and metabolic study of zonal myocardial ischemia in coronary heart disease. Circulation (5) : 834–846, May 1967.

(61) HEYDEN-STUCKY, S. SCHIBLER-REICH, S. Cardiologische Risikofaktoren bei Schweizer Mannern. Schweizerische Medizinische Wochenscrift 97 (1) : 20–25, January 7, 1967.

(62) HEYDEN-STUCKY, S. Epidemiologie des Herzinfarktes 1965. Schweizerische Medizinische Wochenschrift 95(45) : 1535–1540, November 6, 1965.

(63) HIGGINS, M. W., KJELSBERG, M. Characteristics of smokers and nonsmokers in Tecumseh, Michigan. II. The distribution of selected physical measurement and physiologic variables and the prevalence of certain diseases in smokers and nonsmokers. American Journal of Epidemiology 86(1) : 60–77, January 1967.

(64) HINKLE, L. E., Jr., WHITNEY, L. H., LEHMAN, E. W., DUNN, J., BENJAMIN, B., KING, R., PLAKUN, A., FLEHINGER, B. Personal Communication, 1968.

(65) HIRAYAMA, T. Smoking in relation to the death rates of 265,118 men and women in Japan. Tokyo, National Cancer Center Research Institute, September 1967. 14 pp.

(66) HOAK, J. C., WARNER, E. D., CONNOR, W. E. Platelets, fatty acids and thrombosis. Circulation Research 20(1) : 11–17, January 1967.

(67) HYAMS, L., SEGI, M., ARCHER, M. Myocardial infarction in the Japanese. A retrospective study. American Journal of Cardiology 20(4) : 549–554, October 1967.

(68) JACKSON, D. H., OBERMAN, A., MITCHELL, R. E., GRAYBIEL, A. Factors contributing to the ballistocardiographic waveform in healthy middle-

aged men. American Journal of Cardiology 20(4): 531–540, October 1967.

(69) KANNEL, W. B., CASTELLI, W. P., MCNAMARA, P. M. Cigararette smoking and risk of coronary heart disease. Epidemiologic clues to pathogenesis: The Framingham Study. In: Wynder, E. L., Hoffmann, D., editors. Toward A Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press)

(70) KANNEL, W. B., CASTELLI, W. P., MCNAMARA, P. M. The coronary profile: 12-year follow-up in the Framingham study. Journal of Occupational Medicine 9(12): 611–619, December 1967.

(71) KANNEL, W. B., DAWBER, T. R., MCNAMARA, P. M. Detection of the coronary-prone adult: The Framingham Study. Journal of the Iowa Medical Society 56(1): 26–34, January 1966.

(72) KEDRA, M., POLESZAK, J., PITERA, A. Wplyw tytoniu na poziom tluszczowcow krwi. Polski Tygodnik Lekarski 20(3): 1452–1554, September 27, 1965.

(73) KERR, J. W., MAC AULAY, I., PIRRIE, R., BRONTE-STEWART, B. Platelet-aggregation by phospholipids and free fatty acids. Lancet 1: 1296–1299, June, 19, 1965.

(74) KERRIGAN, R., JAIN, A. C., DOYLE, J. T. The circulatory response to cigarette smoking at rest and after exercise. American Journal of the Medical Sciences 255: 113–119, February 1968.

(75) KERSHBAUM, A. Personal communication. March 1968.

(76) KERSHBAUM, A., BELLET, S. Cigarette, cigar, and pipe smoking: Some differences in biochemical effects. Geriatrics 23: 126–134, March 1968.

(77) KERSHBAUM, A., BELLETT, S., CAPLAN, R. F., FEINBERG, L. J. Effect of cigarette smoking on free fatty acids in patients with healed myocardial infarctions. American Journal of Cardiology 10(2): 204–208, August 1962.

(78) KERSHBAUM, A., BELLET, S., DICKSTEIN, E. R., FEINBERG, L. J. Effect of cigarette smoking and nicotine on serum free fatty acids. Based on a study in the human subject and the experimental animal. Circulation Research 9(5): 631–638, May 1961.

(79) KERSHBAUM, A., BELLET, S., HIRABAYASHI, M., FEINBERG, L. J. Regular filter-tip, and modified cigarettes. Nicotine excretion, free fatty acid mobilization, and catecholamine excretion. Journal of the American Medical Association 201(7): 545–546, August 14, 1967.

(80) KERSHBAUM, A., BELLET, S., HIRABAYASHI, M., FEINBERG, L. J., EILBERG, R. Effect of cigarette, cigar and pipe smoking on nicotine excretion. The influence of inhaling. Archives of Internal Medicine 120(3): 311–314, September 1967.

(81) KERSHBAUM, A., BELLETT, S., JIMENEZ, J., FEINBERG, L. J. Differences in effects of cigar and cigarette smoking on free fatty acid mobilization and catecholamine excretion. Journal of the American Medical Association 195(13): 1095–1098, March 28, 1966.

(82) KERSHBAUM, A., BELLET, S., KHORSANDIAN, R. Elevation of serum cholesterol after administration of nicotine. American Heart Journal 69(2): 206–210, February 1965.

(83) KERSHBAUM, A., JIMENEZ, J., BELLET, S., ZANUTTINI, D. Modification of nicotine-induced hyperlipidemia by antiadrenergic agents. Journal of Atherosclerosis Research 6: 524–530, 1966.

(84) KERSHBAUM, A., KHORSANDIAN, R., CAPLAN, R. F., BELLET, S., FEINBERG, L. J. The role of catecholamines in the free fatty acid response to cigarette smoking. Circulation 28(1): 52–57, July 1963.

(85) KERSHBAUM, A., OSADA, H., SCRIABINE, A., BELLET, S., PAPPAJOHN, D. J. Influence of nicotine on the mobilization of free fatty acids from rat adipose tissue *in vitro* and in the isolated perfused dog limb. Circulation 36 (Supplement II) : 20, October 1967.

(86) KERSHBAUM, A., PAPPAJOHN, D. J., BELLET, S., HIRABAYASHI, M., SHAFIIHA, H. Effect of smoking and nicotine on adrenocortical secretion. Journal of the American Medical Association 203(4) : 275–278, January 1968.

(87) KERSHBAUM, A., PAPPAJOHN, J., OSADA, H. BELLET, S. The influence of tobacco smoking on the crystallization of cholesterol. (Abstract) Clinical Research 15(2) : 322, April 1967.

(88) KEYES, M. MIZUKAMI, H. LUMRY, R. Equilibrium measurement in the reactions of heme-proteins with gaseous ligands. Analytical Biochemistry 18: 126–142, 1967.

(89) KINGSBURY, K. J., JARRETT, R. J. Effects of adrenaline and of smoking in patients with peripheral atherosclerotic vascular disease. Lancet 2(7505) : 22–23, July 1, 1967.

(90) KLENSCH, H. Blut-Kathecholamine und -Fettsauren beim Stress durch Rauchen und durch korperliche Arbeit. Zeitschrift fur Kreislaufforschung 55(10) : 1035–1044, October 1966.

(91) KLENSCH, H., SPECKMANN, K., MAETZEL, F. W., MEYER, J. D. Der Plasma-Noradrenalinspiegel bei Koronarkranken in Ruhe und im Nikotin-Stress. Zeitschrift fur Kreislaufforschung 56(12) : 1164–1169, December 1967.

(92) KONTTINEN, A., RAJASALMI, M. Effect of heavy cigarette smoking on postprandial triglycerides, free fatty acids, and cholesterol. British Medical Journal 1(5334) : 850–852, March 30, 1963.

(93) KUHN, R. A. Mode of action of tobacco smoke inhalation upon the cerebral circulation. Annals of the New York Academy of Sciences 142 (Article 1) : 67–71, March 15, 1967.

(94) KULLER, L., LILIENFELD, A. Epidemiological study of sudden and unexpected deaths due to arteriosclerotic heart disease. Circulation 34: 1056–1068, December 1966.

(95) KURIEN, V. A., OLIVER, M. F. Serum-free-acids after acute myocardial infarction and cerebral vascular occlusion. Lancet 2: 122–127, July 16, 1966.

(96) LANE, N. E., OBERMAN, A. The thousand aviator study: Smoking history correlates of selected physiological, biochemical, and anthropometric measures. U.S. Naval Aerospace Medical Institute, NAMI–961. Under the Joint sponsorship of the U.S. Public Health Service, and the National Aeronautics and Space Administration, NASA Order R–136, April 27, 1966. 12 pp.

(97) LEREN, P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. Acta Medica Scandinavica (Supplement 466) : 1–92, 1966.

(98) LIKOFF, W., SEGAL, B. L., KASPARIAN, H. Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. New England Journal of Medicine 276(19) : 1063–1066, May 11, 1967.

(99) LUKE, J. L., HELPERN, M. Sudden unexpected death from natural causes in young adults. A review of 275 consecutive autopsied cases. Archives of Pathology 85(1) : 10–17, January 1968.

(100) MCDONOUGH, J. R., HAMES, G. G., GARRISON, G. E., STULB, S. G., LICHTMAN, M. A., HEFELFINGER, D. C. The relationship of hematocrit to cardiovas-

cular states of health in the Negro and white population of Evans County, Georgia. Journal of Chronic Diseases 18(3) : 243–257, March 1965.

(*101*) MAHADEVAN, V., SINGH, H., LUNDBERG, W. O. Effects of saturated and unsaturated fatty acids on blood platelet aggregation *in vitro*. Proceedings of the Society for Experimental Biology and Medicine 121 : 82–85, 1966.

(*102*) MAHLER, R. Diabetes and arterial lipids. Quarterly Journal of Medicine 34(136) : 484, 1965.

(*103*) MALHOTRA, S. L. Serum lipids, dietary factors and ischemic heart disease. American Journal of Clinical Nutrition 20: 462–474, May 1967.

(*104*) MEYER, J. S. Personal communication. 1968.

(*105*) MOSES, D. C., POWERS, D., SOLOFF, L. A. Glucose blockage of the increase in stroke volume produced by smoking. Circulation 29(6) : 820–844, June 1964.

(*106*) MULCAHY, R., HICKEY, N. J. Cigarette smoking habits of patients with coronary heart disease. British Heart Journal 28 : 404–408, 1966.

(*107*) MULCAHY, R., HICKEY, N. J. The role of cigarette smoking in the causation of atherosclerosis. Geriatrics 22(2) : 165–174, February 1967.

(*108*) MULCAHY, R., HICKEY, N. J., MAURER, B. J. The aetiology of coronary heart disease in women. Journal of the Irish Medical Association 60 (335) : 23–29, January 1967.

(*109*) MULCAHY, R., HICKEY, N. J., MAURER, B. J. Coronary heart disease in women. Study of risk factors in 100 patients less than 60 years of age. Circulation 36(4) : 577–586, April 1967.

(*110*) MURCHISON, L. E., FYFE, T. Effects of cigarette smoking on serum-lipids, blood glucose, and platelet adhesiveness. Lancet 2(7456) : 182–184, July 23, 1966.

(*111*) MURPHY, E. A., MUSTARD, J. F. Smoking and thrombosis. In: Wynder, E. L. Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press)

(*112*) NADEAU, R. A., JAMES, T. N. Effects of nicotine on heart rate studies by direct perfusion of sinus node. American Journal of Physiology 212(4) : 911–916, April 1967.

(*113*) NATVIG, H. Effekten av umettede fettsyrer pa hyppigheten av hjerteinfarkt M.M. Resultatet av bedriftslegenes "oljeforsok." Tidsskrift for den Norske Laegeforening 87(11) : 1033–1041, June 1967.

(*114*) NIKKILA, E. A., VESENNE, M–R., MIETTINEN, T. A., PELKONEN, R. Plasma-insulin in coronary heart disease: Response to oral and intravenous glucose and to tolbutamide. Lancet 2: 508–511, September 11, 1965.

(*115*) PAGE, I. H., LEWIS, L. A., MOINUDDIN, M. (Clinical Notes) Effect of cigarette smoking on serum cholesterol and lipoprotein concentrations. Journal of the American Medical Association 171(11) : 1500–1502, November 14, 1959.

(*116*) PAPACOSTAS, C. A., REED, J. P. Influence of beta receptor blockade on certain cardiovascular actions of nicotine. Archives Internationales de Pharmacodynamie et de Therapie 164(1) : 167–172, 1966.

(*117*) PENTECOST, B., SHILLINGFORD, J. The acute effects of smoking on myocardial performance in patients with coronary arterial disease. British Heart Journal 26: 422–429, 1964.

(*118*) PETERS, N., HALES, C. N. Plasma-insulin concentrations after myocardial infarction. Lancet 1: 1144–1145, May 29, 1965.

(119) PINCHERLY, G., WRIGHT, H. B. Screening in the early diagnosis and prevention of cardiovascular disease. Journal of the College of General Practitioners 13: 280–289, 1967.

(120) PURI, P. S., ALAMY, D., BING, R. J., Effect of nicotine on the contractility of the intact heart. Journal of Clinical Pharmacology, 1968. (In press)

(121) PURI, P. S., BING, R. J. Influnce of cardiovascular drugs on the force-velocity relation of the intact heart. The Physiologist 10(3): 285, August 1967.

(122) REID, D. D., HOLLAND, W. W., ROSE, G. A. An Anglo-American cardiovascular comparison. Lancet 4(7531): 1375–1378, December 30, 1967.

(123) ROSENMAN, R. H., FRIEDMAN, M., JENKINS, C. D., STRAUS, R., WURM, M., KOSITCHEK, R. Clinically unrecognized myocardial infarction in the Western Collaborative Group Study. American Journal of Cardiology 19(6): 776–782, June 1967.

(124) ROSENMAN, R. H., FRIEDMAN, M., JENKINS, C. D., STRAUS, R., WURM, M., KOSITCHEK, R. Recurring and fatal myocardial infarction in the Western Collaborative Group Study. American Journal of Cardiology 19(6): 771–775, June 1967.

(125) ROSENMAN, R. H., FRIEDMAN, M., JENKINS, C. D., ZYZANSKI, S. J. Personal Communication, 1968.

(126) ROSSI-FANELLI, A., ANTONINI, E. Studies on the oxygen and carbon monoxide equilibria of human myoglobin. Archives of Biochemistry and Biophysics 77: 478–492, 1958.

(127) ROTH, O., BERKI, A., WOLFF, G. D. Long range observations in fifty-three young patients with myocardial infarction. American Journal of Cardiology 19(3): 331–338, March 1967.

(128) ROWSELL, H. C., HEGARDT, B., DOWNIE, H. G., MUSTARD, J. F., MURPHY, E. A. Adrenaline and experimental thrombosis. British Journal of Haematology 12(1): 66–73, 1966.

(129) SELTZER, C. C. An evaluation of the effect of smoking on coronary heart disease. I. Epidemiological evidence. Journal of the American Medical Association 203(3): 193–200, January 15, 1968.

(130) SEN GUPTA, A. N., GHOSH, B. P. Observations on some cardiovascular and biochemical effects of tobacco smoking in health and in ischaemic cardiacs. Bulletin of the Institute of Post-Graduate Medical Education and Research 9(2): 45–57, April 1967.

(131) SHANKS, R. G. The pharmacology of beta sympathetic blockade. American Journal of Cardiology 18(9): 308–316, September 1966.

(132) SHIBATA, S., HOLLANDER, P. H., WEBB, J. L. Effect of nicotine on the transmembrane potential and contractility of isolated rat atria. Experientia 24(3): 236–237, 1968.

(133) SHIMAMOTO, T., ISHIOKA, T., Release of a thromboplastic substance from arterial walls by epinephrine. Circulation Research 12(2): 138–144, February 1963.

(134) SIEVERS, M. L. Myocardial infarction among southwestern American Indians. Annals of Internal Medicine 67(4): 800–807, October 1967.

(135) SLEIGHT, P. A cardiovascular depressor reflex from the epicardium of the left ventricle in the dog. Journal of Physiology 173(3): 321–343, 1964.

(136) SOLOFF, L. A., SCHWARTZ, H. Relationship between glucose and fatty acid in myocardial infarction. Lancet 1: 449–452, February 26, 1966.

(137) STABLES, D. P., RUBENSTEIN, A. H., METZ, J., LEVIN, N. W. The possible role of hemoconcentration in the etiology of myocardial infarction. American Heart Journal 73(2): 155–159, February 1967.

(*138*) STAMLER, J., BERKSON, D. M., LEVINSON, M., LINDBERG, H. A., MOJONNIER, L., MILLER, W. A., HALL, Y., ANDELMAN, S. L. Coronary artery disease. Status of preventive efforts. Archives of Environmental Health 13(3): 322–335, September 1966.

(*139*) STARR, I. The place of the ballistocardiogram in a Newtonian cardiology; and the new light it sheds on certain old clinical problems. Proceedings of the Royal Society of Medicine 60: 1297–1306, December 1967.

(*140*) STROBEL, M., GSELL, O. Mortalitat in Beziehung zum Tabakrauchen: 9 Jahre Beobachtungen bei Arzten in der Schweiz. Helvetica Medica Acta 32(6): 547–593, December 1965.

(*141*) SZANTO, S. Smoking and atherosclerosis. British Medical Journal 3: 178, July 15, 1967.

(*142*) TAYLOR, R. R., CINGOLANI, H. E., GRAHAM, J. P., CLANCY, R. L. Myocardial oxygen consumption: left ventricular fibre shortening and wall tension. Cardiovascular Research 1: 219–228, 1967.

(*143*) THOMAS, C. B. On cigarette smoking, coronary heart disease, and the genetic hypothesis. Johns Hopkins Medical Journal 122(2): 69–76, February 1968.

(*144*) TIBBLIN, G. High blood pressure in men aged 50—A population study of men born in 1913. Acta Medica Scandinavica (Supplementum 470): 1–84, 1967.

(*145*) TRUETT, J., CORNFIELD, J., KANNEL, W. A multivariate analysis of the risk of coronary heart disease in Framingham. Journal of Chronic Diseases 20: 511–524, 1967.

(*146*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Public Health Service Review: 1967. Washington, U.S. Department of Health, Education and Welfare, Public Health Service Publication No. 1696, 1967. 227 pp.

(*147*) U.S. PUBLIC HEALTH SERVICE. National Center for Health Statistics. Monthly Vital Statistic Report. Final Mortality Statistics 16(2) (Supplement): 1–12, March 12, 1968.

(*148*) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service, Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.

(*149*) VALLANCE-OWEN, J. Comments on Dr. Mahler's "Diabetes and Arterial Lipids"). Quarterly Journal of Medicine 34(136): 485, October 1965.

(*150*) VAN BUCHEM, F. S. P. Serum lipids, nutrition and atherosclerotic complications in man. Acta Medica Scandinavica 181(4): 403–461, April 1967.

(*151*) VILLIGER, U., HEYDEN-STUCKY, S. Das Infarktprofil. Unterschiede zwischen infarktpatienten und Kontrollpersonen in der Ostschweiz. Schweizerische Medizinische Wochenschrift 96(23): 748–758, June 11, 1966.

(*152*) WAHLBERG, F. The intravenous glucose tolerance test in atherosclerotic disease with special reference to obesity hypertension, diabetic heredity and cholesterol values. Acta Medica Scandinavica 171(1): 1–7, 1962.

(*153*) WARNER, E. D. HOAK, J. C., CONNOR, W. E. The role of fatty acids in platelet aggregation and thrombosis. In: Brinkland, K. M., editor. Platelets: Their Role in Hemostasis and Thrombosis. Chapter 24. Transactions of the Conference held under the auspices of the International Committee on Haemostasis and Thrombosis, Chapel Hill, North Carolina, December 1966. Pp. 249–259.

(154) WEBB, W. R., WAX, S. D., SUGG, W. L. Cigarette smoke and fibrillation threshold in dogs. Clinical Research 16(1) : 74, January 1968.

(155) WEINBLATT, E. Personal communication. April 1968.

(156) WEISSLER, A. M., KRUGER, F. A., BABA, N., SCARPELLI, D. G., LEIGHTON, R. F., GALLIMORE, J. K. Role of anaerobic metabolism in the preservation of functional capacity and structure of anoxic myocardium. Journal of Clinical Investigation 47 : 403–416, 1968.

(157) WELBORN, T. A., BRECKENRIDGE, A., RUBENSTEIN, A. H., DOLLERY, C. T., FRASER, T. R. Serum-insulin in essential hypertension and in peripheral vascular disease. Lancet 1(7451) : 1336–1337, June 18, 1966.

(158) WESTFALL, T. C., CIPOLLONI, P. B., EDMUNDOWICZ, A. C. Influence of propranolol on hemodynamic changes and plasma catecholamine levels following cigarette smoking and nicotine. Proceedings of the Society for Experimental Biology and Medicine 123 : 174–179, 1966.

(159) WITTENBERG, J. B. The molecular mechanism of hemoglobin-facilitated oxygen diffusion. Journal of Biological Chemistry 241(1) : 104–114, January 10, 1966.

(160) YAMAMOTO, T. The effect of propranolol on the haemodynamic changes caused by cigarette smoking. Japanese Circulation Journal 31(12) : 1958, December 1967.

SUPPLEMENTAL CARDIOVASCULAR REFERENCES

S1. ANTONINI, E. Hemoglobin and its reaction with ligands. Science 158(3807) : 1417–1425, December 15, 1967.

S2. ARMITAGE, A. K. Effects of nicotine and tobacco smoke on blood pressure and release of catecholamines from the adrenal glands. British Journal of Pharmacology and Chemotherapy 25 : 515–526, October 1965.

S3. ARMITAGE, A. K., MILTON, A. S., MORRISON, C. F. Effects of nicotine and some nicotine-like compounds injected into the cerebral ventricles of the cat. Journal of Physiology (London) 181 : 30P–31P, 1965.

S4. AVIADO, D. M., JR., SCHMIDT, C. F. Cardiovascular and respiratory reflexes from the left side of the heart. American Journal of Physiology 196(4) : 726–730, 1959.

S5. BARER, G. R., HOWARD, P., MCCURRIE, J. R. The effect of carbon dioxide and changes in blood pH on pulmonary vascular resistance in cats. Clinical Science 32 : 361–376, 1967.

S6. BEARD, R. R., WERTHEIM, G. A. Behavioral impairment associated with small doses of carbon monoxide. American Journal of Public Health and the Nation's Health 57(11) : 2012–2022, November 1967.

S7. BECKETT, A. H., TRIGGS, E. J. Enzyme induction in man caused by smoking. Nature 216(5115) : 587, November 11, 1967.

S8. BELLET, S. Adrenergic effects of nicotine on coronary blood flow and blood lipids. IN : Raab, W., editor. Prevention of Ischemic Heart Diseases. Principles and Practice. Springfield, C.C. Thomas, 1966. Pp. 74–84.

S9. BELLET, S., WEST, J. W., MULLER, O. T., MANZOLI, U. C. Effect of nicotine on the coronary blood flow and related circulatory parameters. Correlative study in normal dogs and dogs with coronary insufficiency. Circulation Research 10(1) : 27–34, January 1962.

S10. BELLI, C., ALBERTINI, E., MARTINESI, L., PELIEGRINI, G. F. Studio sperimentale di momenti dell'emocagulazione e della fibrinolisi in corso d'intossicazione nicotinica caronica. Archivio per le Scienze Mediche 120 (6) : 460–478, December 1965.

S11. BING, R. J., COHEN, A., BLUEMCHEN, G. Tobacco alkaloids and circulation. In: Von Euler, U.S., editor. Tobacco Alkaloids and Related Compounds. Proceedings of the Fourth International Symposium held at the Wenner-Gren Center, Stockholm, February 1964. New York, MacMillan, 1965. Pp. 241–251.

S12. BLASCHKO, H., HAGEN, P., WELCH, A. D. Observations on the intracellular granules of the adrenal medulla. Journal of Physiology (London) 129: 27–49, 1955.

S13. BOELLING, G. M., PHILLIPS, W. J., FREEKING, H. W., PAINE, R. Roentgenographic exercise test. A new test of myocardial state. Journal of the American Medical Association 202(4): 275–278, October 23, 1967.

S14. BRITMAN, N. Z., LEVINE, H. J. Contractile element work: a major determinant of myocardial oxygen consumption. Journal of Clinical Investigation 43(7): 1397–1408, July 1964.

S15. BROX, D., SELVAAG, O. The effect of erythritol-tetra-nicotinate on serum-cholesterol levels in man. Acta Medica Scandinavica 182(4): 437–444, 1967.

S16. BURT, R. L. Plasma nonesterified fatty acids in normal pregnancy and the puerperium. Obstetrics and Gynecology 15(4): 460–464, April 1960.

S17. BUTKUS, A., PAGE, I. H. Smoking and postabsorptive serum lipid levels. Journal of the American Medical Association 192(1): 52–53, April 5, 1965.

S18. BYGDEMAN, S., ELIASSON, R., JOHNSON, S. R. Relationship between postoperative changes in adenosine-diphosphate induced platelet adhesiveness and venous thrombosis. Lancet 1: 1301–1302, June 11, 1966.

S19. BYRD, R. B., DIVERTIE, M. B., SPITTELL, J. A., JR. Bronchogenic carcinoma and thromboembolic disease. Journal of the American Medical Association 202(11): 1019–1022, December 11, 1967.

S20. CAPRON, P. Essai d'interprétation des balistocardiogrammes en fonction des traces synchrones type Blomberger. In: Knopp, A.A., editor. Ballistocardiography and Cardiovascular Dynamics. Proceedings, 1st World Congress, Amsterdam, 1965. New York, Karger, 1966. Pp. 155–162.

S21. CHRISTAKIS, G. J., RINZLER, S. H., ARCHER, M., HASHIM, S. A., VAN ITALLIE, T. B., MAO, P. Effect of a serum cholesterol-lowering diet on composition of depot fat in man. American Journal of Clinical Nutrition 16: 243–251, February 1965.

S22. CHRISTAKIS, G., RINZLER, S. H., ARCHER, M., WINSLOW, G., JAMPEL, S., STEPHENSON, J., FRIEDMAN, G., FEIN, H., KRAUS, A., JAMES, G. The anti-coronary club. A dietary approach to the prevention of cornary heart disease—a seven-year report. American Journal of Public Health and the Nation's Health 56(2): 299–314, February 1966.

S23. CLANCY, R. L., GRAHAM, T. P., JR., POWELL, W. J., JR., GILMORE, J. P. Inotropic augumentation of myocardial oxygen consumption. American Journal of Physiology 212(5): 1055–1061, May 1967.

S24. COBURN, R. F., FORSTER, R. E., KANE, P. B. Considerations of the physiological variables that determine the blood carboxyhemoglobin concentration in man. Journal of Clinical Investigation 44(11): 1899–1910, November 1965.

S25. COBURN, R. F., WILLIAMS, W. J., WHITE, P., KAHN, S. B. The production of carbon monoxide from hemoglobin *in vivo*. Journal of Clinical Investigation 46(3): 346–356, March 1967.

S26. CONNOR, W. E., HOAK, J. C., WARNER, E. D. Massive thrombosis produced by fatty acid infusion. Journal of Clinical Investigation 42(6): 860–866, June 1963.

S27. DALDERUP, L. M. Vitamin D, cholesterol, and calcium. (Letter) Lancet 1: 645, March 23, 1968.

S28. DALE, H. H. Nomenclature of fibres in the autonomic system and their effects. Journal of Physiology (London) 80:10P–11P, 1933/1934.

S29. DEBRUIN, A. Carboxyhemoglobin levels due to traffic exhaust. Archives of Environmental Health 15(3): 384–389, September 1967.

S30. DECAMP, P. T., CARRERA, A. E., OCHSNER, A., Jr., The hypercoagulable state. Surgery 63(1): 173–180, January 1968.

S31. DECKER, K., SAMMECK, R. Enzymchemische Untersuchungen zum Nicotinabbau in der Kaninchenleber. Biochemische Zeitschrift 340(3): 326–336, August 1964.

S32. DHALLA, N. S., MCLAIN, P. L. Effect of cardio-active drugs on the rate, contractile force and phosphorylase activity in frog heart. Archives Internationales de Pharmacodynamie et de Therapie 163(2): 272–283, 1966.

S33. DOMINO, E. F. Electroencephalographic and behavioral arousal effects of small doses of nicotine: A neuropsychopharmacological study. Annals of the New York Academy of Sciences 142(Article 1): 216–244, March 15, 1967.

S34. DOYLE, J. T. Etiology of coronary disease. Risk factors influencing coronary disease. Modern Concepts of Cardiovascular Disease 35(4): 81–86, April 1966.

S35. ECCLES, R. M., LIBET, B. Origin and blockade of the synaptic responses of curarized sympathetic ganglia. Journal of Physiology (London) 157: 484–503, 1961.

S36. EDWARDS, M. J., RIGAS, D. A. Electrolyte-labile increase of oxygen affinity during *in vivo* aging of hemoglobin. Journal of Clinical Investigation 45(10): 1579–1588, October 1967.

S37. EL-EBRASHY, N., EL-ASHNAWY, S., ALY, A. Effect of smoking on the index of platelet adhesiveness and blood glucose level in atherosclerotic patients. Journal of the Egyptian Medical Association 50(3): 157–168, 1967.

S38. ELIAKIS, C., COUTSELINIS, A., ELIAKIS, E. Depistage des fumeurs par le dosage des thiocyanures dans le sang: Contribution au diagnostic etiologique de l'oxycarbonisme chronique. Annales de Medecine Legale 47(4): 327–329, July–August 1967.

S39. EMMONS, P. R., HARRISON, M. J. G., HONOUR, A. J., MITCHELL, J. R. A. Effect of dipyridamole on human platelet behaviour. Lancet 2: 603–606, September 25, 1965.

S40. ENGELBERG, H., FUTTERMAN, M. Cigarette smoking and thrombotic coagulation of human blood. Further *in vitro* studies. Archives of Environmental Health 14(2): 266–270, February 1967.

S41. FODOR, J. T., GLASS, L. H., WEINER, J. M. Summary of findings: Immediate effects of smoking. Northridge, California, San Fernando Valley State College, Health Science Research Center, September 8, 1967. [Unpublished]

S42. FORBES, W. H., SARGENT, F., ROUGHTON, F. J. W. The rate of carbon monoxide uptake by normal men. American Journal of Physiology 143: 594–608, 1945.

S43. FRIEDMAN, M., ROSENMAN, R. H., BYERS, S. Serum lipids and conjunctival circulation after fat ingestion in men exhibiting Type–A behavior pattern. Circulation 29: 874–886, June 1964.

S44. FUREY, S. A., SCHAANNING, J., SPOONT, S., BIRKHEAD, N. C. The comparative effects on circulation of smoking tobacco and lettuce leaf cigarettes. Angiology 18(4) : 218–223, April 1967.

S45. GARLAND, H., PEARCE, J. Neurological complications of carbon monoxide poisoning. Quarterly Journal of Medicine 36(144) : 445–455, October 1967.

S46. GOLDSMITH, J. R., TERZAGHI, J., HACKNEY, J. D. Evaluation of fluctuating carbon monoxide exposures. Theoretical approach and a preliminary test of methods for studying effects on human populations of fluctuating exposures from multiple sources. Archives of Environmental Health 7(6) : 647–663, December 1963.

S47. GOLDSTEIN, L., BECK, R. A. Amplitude analysis of the electroencephalogram. Review of the information obtained with the integrative method. International Review of Neurobiology 8 : 265–312, 1965.

S48. HOAK, J. C., CONNOR, W. E., ECKSTEIN, J. W., WARNER, E. D. Fatty acid-induced thrombosis and death : Mechanisms and prevention. Journal of Laboratory and Clinical Medicine 63(5) : 791–800, May 1964.

S49. HOAK, J. C., CONNOR, W. E., WARNER, E. D. Thrombogenic effects of albumin-bound fatty acids. Archives of Pathology 81(2) : 136–139, February 1966.

S50. HOAK, J. C., POOLE, J. C. F., ROBINSON, D. S. Thrombosis associated with mobilization of fatty acids. American Journal of Pathology 43(6) : 987–998, December 1963.

S51. HOFF, E. C., HOCKMAN, C. H. Neurophysiological aspects of the action of nicotine. Annals of the New York Academy of Sciences 142 (Article 1) : 121–125, March 15, 1967.

S52. IRVING, D. W., YAMAMOTA, T. Cigarette smoking and cardiac output. British Heart Journal 25 : 126–132, 1963.

S53. KEDRA, M., DMOWSKI, G. The influence of tobacco smoking on the development of atherosclerosis and on the composition of blood lipids. Polish Medical Journal 5(1) : 37–43, 1966.

S54. KERSHBAUM, A., BELLET, S. Cigarette smoking and blood lipids. Journal of the American Medical Association 187(1) : 32–36, January 4, 1964.

S55. KERSHBAUM, A., BELLET, S. Smoking as a factor in atherosclerosis. A review of epidemiological, pathological, and experimental studies. Geriatrics 21(12) : 155–170, December 1966.

S56. KERSHBAUM, A., PAPPAJOHN, D. J., BELLET, S., HIRABAYASHI, M., SHAFIIHA, H. Effect of smoking and nicotine on adrenocortical secretion. Clinical Research 15 : 261, April 1967.

S57. KIEN, G. A., LASKER, N., SHERROD, T. R. Action of cigarette smoke on cardiovascular hemodynamics and oxygen utilization in the dog. Journal of Pharmacology and Experimental Therapeutics 124 : 35–42, 1958.

S58. KIRKEBY, K. Blood lipids, lipoproteins, and proteins in vegetarians. Acta Medica Scandinavica (Supplement 443) : 1–84, 1966.

S59. KULLER, L., LILIENFELD, A., FISHER, R. Sudden and unexpected deaths in young adults. An epidemiological study. Journal of the American Medical Association 198(3) : 248–252. October 17, 1966.

S60. KONTTINEN, A. Cigarette smoking and serum lipids in young men. British Medical Journal 1 : 1115–1116, April 21, 1962.

S61. LAFRENZ, M. EKG–Veränderungen und begünstigende Faktoren des Angina-pectoris-Syndroms. Zeitschrift fur die Gesamte Innere Medizin und ihre Grenzgebiete 22(23) : 773–780, December 1, 1967.

S62. LANGLEY, J. N., DICKINSON, W. L. III. On the local paralysis of peripheral ganglia, and on the connection of different classes of nerve fibres with

them. Proceedings of the Royal Society; Series B: Biological Sciences 46: 423–431, November 21, 1889.

S63. LELLOUCH, J., BEAUMONT, J. L. Enquete epidemiologique sur l'Atherosclerose. Chapitre III. La tension arterielle: distribution et correlations dans ungroupe professionnel. Bulletin de l'Institut National de la Recherche Medicale 22(2): 203–214, March–April 1967.

S64. LILIENTHAL, J. L., Jr., FUGITT, C. H. The effect of low concentrations of carboxyhemoglobin on the "altitude tolerance" of man. American Journal of Physiology 145: 359–364, 1946.

S65. LUCCHESI, B. R., SCHUSTER, C. R., EMLEY, G. S. The role of nicotine as a determinant of cigarette smoking frequency in man with observations of certain cardiovascular effects associated with the tobacco alkaloid. Clinical Pharmacology and Therapeutics 8(6): 789–796, November–December 1967.

S66. MCDONOUGH, J. R., HAMES, C. G., GARRISON, G. E., STULB, S. C., LICHTMAN, M. A., HEFELFINGER, D. C. The relationship of hematocrit to cardiovascular states of health in the Negro and white population of Evans County, Georgia. Journal of Chronic Diseases 18(3): 243–257, March 1965.

S67. MCFARLAND, R. A. Tobacco and efficiency. In: Human Factors in Air Transportation, Occupational Health and Safety. New York, McGraw-Hill, 1953. Pp. 299–307.

S68. MCFARLAND, R. A., MOORE, R. C. Human factors in highway safety. A review and evaluation. New England Journal of Medicine 256: 792–799, 837–845, 890–897, April 25, May 2 and 9, 1957.

S69. MCFARLAND, R. A., MOSELEY, A. L. Carbon monoxide in trucks and buses and information from other areas of research on carbon monoxide, altitude and cigarette smoking. In: Conference Proceedings: Health, medical and drug factors in highway safety. Washington, National Academy of Sciences—National Research Council Publication No. 328, 1954. Pp. 4.17–4.33.

S70. MCFARLAND, R. A., ROUGHTON, F. J. W., HALPERIN, M. H., NIVEN, J. I. The effects of carbon monoxide and altitude on visual thresholds. Journal of Aviation Medicine 15(6): 381–394, December 1944.

S71. MCKENNIS, H., Jr., TURNBULL, L. B., BOWMAN, E. R. N-methylation of nicotine and cotinine *in vivo*. Journal of Biological Chemistry 238(2): 719–723, February 1963.

S72. MIHOCZY, L. Pulmonary hypertension and BCG. In: Knoop, A. A., editor. Ballistocardiography and Cardiovascular Dynamics. Proceedings, 1st World Congress, Amsterdam, 1965. New York, Karger, 1966. Pp. 265–269.

S73. MILLER, R. L., STEDMAN, R. L. Essential absence of beta-naphthylamine in cigarette smoke condensate. Tobacco 165(8): 32, August 25, 1967.

S74. MISIRLIOGLU, Y. I. Prevention and cure of arteriosclerosis, essential hypertension by activation of fibrinogenolysis with coenzymes; a new, reliable, simple diagnostic test for arteriosclerosis. Summary 19: 1–14, December 1967.

S75. MORRIS, W. H. M. Heart disease in farm workers. Canadian Medical Association Journal 96: 821–824, March 25, 1967.

S76. MURPHREE, H. B., PFEIFFER, C. C., PRICE, L. M. Electroencephalographic changes in man following smoking. Annals of the New York Academy of Sciences 142(Article 1): 245–260, March 15, 1967.

S77. Oberman, A., Lane, N. E., Harlan, W. R., Graybiel, A., Mitchell, R. E. Trends in systolic blood pressure in the thousand aviator cohort over a twenty-four year period. Circulation 36(10) : 812–822, December 1967.

S78. Ogston, D., Fullerton, H. W. Plasma fibrinolytic activity following recent myocardial and cerebral infarction. Lancet 2: 99–101, July 17, 1965.

S79. Oram, S. Smoking and ischaemic heart disease. British Heart Journal 30(2) : 145–150, March 1968.

S80. Oram, S., Sowton, E. Tobacco angina. Quarterly Journal of Medicine, New Series 32(126) : 115–143, April 1963.

S81. Pfeiffer, C. C., Beck, R. A., Goldstein, L. The modification of central nervous system (CNS) function by autonomic drugs. Amine shift responses differentiate between CNS nicotinic and muscarinic effects. Annals of the New York Academy of Sciences 142(Article I) : 181–189, March 15, 1967.

S82. Pincherle, G., Shanks, J. Haemoglobin values in business executives. British Journal of Preventive and Social Medicine 21(1) : 40–42, January 1967.

S83. Pincherle, G., Shanks, J. Value of the erythrocyte sedimentation rate as a screening test. British Journal of Preventive and Social Medicine 21(3) : 133–136, July 1967.

S84. Rakusan, K., Du Mesnil De Rochemont, W. Hanlon, J., Braasch, W., Tschopp, H., Bing, R. J. Effect of nicotine and vasopressin on capillary blood flow and capacity of the terminal vascular bed. Medicina et Pharmacologia Experimentalis 17(2) : 119–128, 1967.

S85. Ramsey, J. M. Carboxyhemoglobinemia in parking garage employees. Archives of Environmental Health 15(5) : 580–583, November 1967.

S86. Regan, T. J., Frank, M. J., McGinty, J. F., Zobl, E., Hellems, H. K., Bing, R. J. Myocardial response to cigarette smoking in normal subjects and patients with coronary disease. Circulation 23(3) : 365–369, March 1961.

S87. Rinzler, S. H., Archer, M., Christakis, G. J. Primary prevention of coronary heart disease by diet. (Annotations) American Heart Journal 73(2) : 287–289, February 1967.

S88. Ripka, O. Epidemiologie des hohen Blutdrucks. Medizinische Klinik 63(3) : 89–93, January 19, 1968.

S89. Rosenman, R. H. Emotional factors in coronary heart disease. Postgraduate Medicine 42(3) : 165–171, September 1967.

S90. Sayers, R. R., Yant, W. P. Levy, E., Fulton, W. B. Effect of repeated daily exposure of several hours to small amounts of automobile exhaust gas. Public Health Bulletin No. 186, 1929. 58 pp.

S91. Schievelbein, H., Peter, H., Trautschold, I., Werle, E., Freisetzung von 5-Hydroxytryptamin aus Thrombocyten durch Harmalin. Biochemical Pharmacology 15 : 195–197, 1966.

S92. Schievelbein, H., Werle, E. Mechanism of the release of amines by nicotine. Annals of the New York Academy of Sciences 142(Article 1) : 72–82, March 15, 1967.

S93. Schilling, F. J., Christakis, G. J. Bennett, N. J., Coyle, J. F. Studies of serum cholesterol in 4,244 men and women: an epidemiological and pathogenetic interpretation. American Journal of Public Heath and the Nation's Health 54(3) : 461–476, March 1964.

S94. SCHIMMLER, W., SCHIMERT, G., NEFF, C. Rauchgewohnheiten und Aortenelastizität. (Messung der Pulswellengeschwindigkeit bei männlichen Zigarettenrauchern, Ex- und Nichtrauchern) Vorläufige Mitteilung. Zeitschrift für Kreislaufforschung 56(11) : 1121–1127, November 1967.

S95. SCHMITERLOW, C. G., HANSSON, E., ANDERSSON, G., APPELGREN, L. S., HOFFMANN, P. C. Distribution of nicotine in the central nervous system. Annals of the New York Academy of Sciences 142(Article 1) : 2–14, March 15, 1967.

S96. SCHULTE, J. H. Effects of mild carbon monoxide intoxication. Archives of Environmental Health 7(5) : 524–530, November 1963.

S97. SHILLINGFORD, J. P. The acute effects of smoking on the performance of the heart in normal subjects and patients with coronary heart disease. In : von Euler, U.S., editor. Tobacco Alkaloids and Related Compounds. New York, Pergamon, 1965. Pp. 263–272.

S98. SIEVERS, M. L. Cigarette and alcohol usage by southwestern American Indians. American Journal of Public Health and the Nation's Health 58(1) : 71–82, January 1968.

S99. SILOVE, E. D., GROVER, R. F. Effects of alpha adrenergic blockade and tissue catecholamine depletion on pulmonary vascular response to hypoxia. Journal of Clinical Investigation 47 : 274–285, 1968.

S100. SINGH, J. Effect of nicotine on blood clotting time of albino rats fed atherogenic diet. Archives Internationales de Pharmacodynamie et de Therapie 154(1) : 221–227, March 1965.

S101. SINGH, J., OESTER, Y. T. Nicotine antagonism with heparin. Possible mode of action on human blood coagulation time *in vitro*. Archives Internationales de Pharmacodynamie et de Therapie 149(3–4) : 354–361, June 1, 1964.

S102. SODI-PALLARES, D., DE MITCHELI, A., MEDRANO, G., FISHLEDER, B., BISTENI, A., FRIEDLAND, C., TESTELLI, M. Effets sur l'electrocariogramme de la solution glucose-insuline-potassium au cours de l'insuffisance coronarienne aigue et chronique. Malattie Cardiovasculari 3(1) : 41–79, 1962.

S103. SONNENBLICK, E. H., ROSS, J., Jr., COVELL, J. W., KAISER, A., BRAUNWALD, E. Velocity of contraction as a determinant of myocardial oxygen consumption. American Journal of Physiology 209(5) : 919–927, May 1965.

S104. SPECKMANN, K., KLENSCH, H., MAETZEL, F. K., MEYER, J. D. Untersuchungen zur Frühdiagnose der Angina Pectoris. Deutsche Medizinische Wochenschrift 92 : 1493–1947, August 25, 1967.

S105. STEIN, P. D., ALSHABKHOUN, S., HATEM, C., PUR-SHAHRIARI, A. A., HAYNES, F. W., HARKEN, D. E., DEXTER, L. Coronary artery blood flow in acute pulmonary embolism. American Journal of Cardiology 21(1) : 32–37, January 1968.

S106. STERN, S., RAPAPORT, E. Comparison of the reflexes elicited from combined or separate stimulation of the aortic and carotid chemoreceptors on myocardial contractility, cardiac output and systemic resistance. Circulation Research 20(2) : 214–227, February 1697.

S107. TALBOT, S. A., HARRISON, W. K., Jr., GINN, W. M., Jr. Features of ULF–BCG pertinent to coronary heart disease. In : Knoop, A. A., editor. Ballistocardiography and Cardiovascular Dynamics. Proceedings, 1st World Congress, Amsterdam, 1965. New York, Karger, 1966. Pp. 55–68.

S108. TALBOTT, G. D. Influence of environmental factors on lipid-response curves. Cigarette smoking, salt, alcohol, and high-fat diet effecting healthy males. Geriatrics 19(8) : 575–584, August 1964.

S109. Taylor, L., Schilling, R. S. F. The health and habits of higher executives. Journal of the Royal College of General Practitioners 14(3): 262–281, November 1967.

S110. Travell, J., Rinzler, S. H., Karp, D. Cardiac effects of nicotine in the rabbit with experimental coronary atherosclerosis. Part VII. Effects of nicotine and smoking in cardiovascular disorders. Annals of the New York Academy of Sciences 90(1): 290–301, September 27, 1960.

S111. Trouton, D., Eysenck, H. The effects of drugs on behavior. In: Eysenck, H. J., editor. Handbook of Abnormal Psychology. New York, Basic Books, 1961. Pp. 634–696.

S112. Wenzel, D. G. Drug-induced cardiomyopathies. Journal of Pharmaceutical Sciences 56(10): 1209–1224, October 1967.

S113. Wenzel, D. G., Kamal, J. S. Turner, J. A. The chronic effects of orally administered nicotine in cholesterol-fed rabbits. Annals of the New York Academy of Sciences 90(1): 302–307, September 27, 1960.

S114. Wertlake, P. T., Wilcox, A. A., Haley, M. I., Peterson, J. E. Relationship of mental and emotional stress to serum cholesterol levels. Proceedings of the Society for Experimental Biology and Medicine 97: 163–165, January 1958.

S115. Westfall, T. C., Anderson, G. P. Influence of nicotine on catecholamine metabolism in the rat. Archives Internationales de Pharmacodynamie et de Therapie 169(2): 421–428, October 1967.

S116. Whelan, R. F. Alcohol, nicotine and man. Medical Journal of Australia 1(3): 77–83, January 20, 1968.

CHAPTER 2

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.

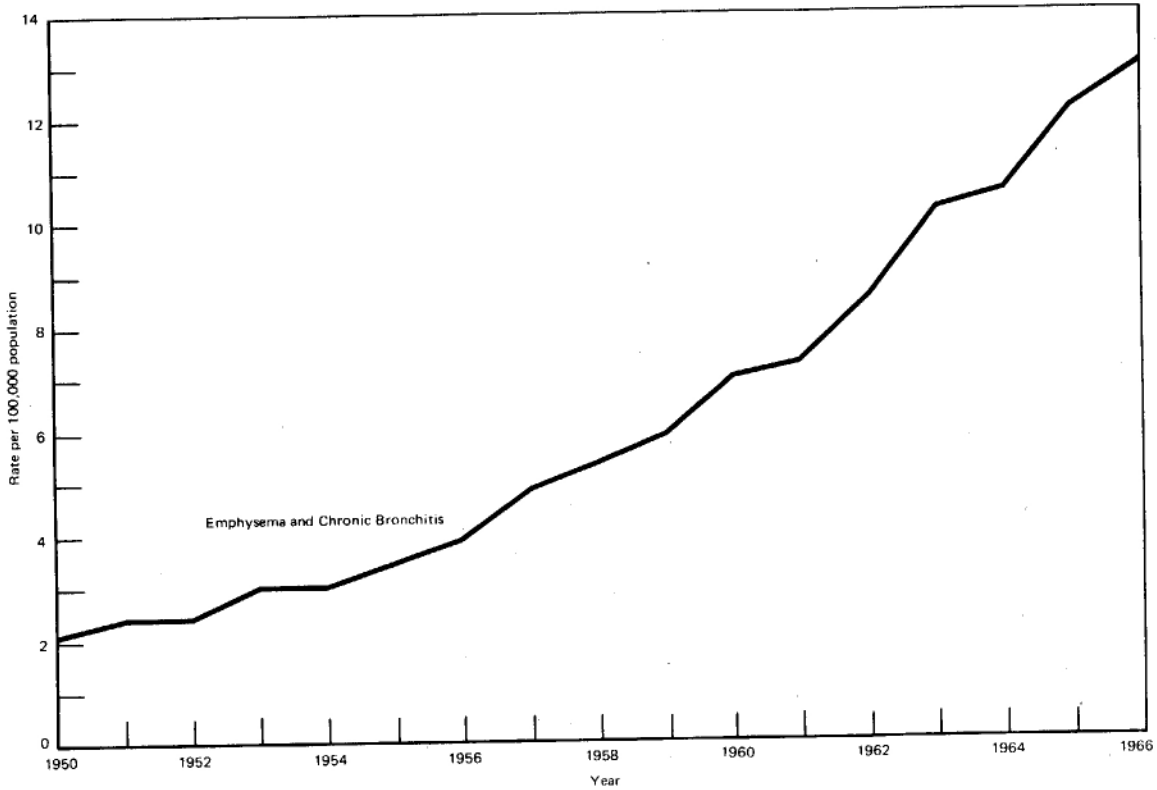

FIGURE 1—Death rates for emphysema and chronic bronchitis. United States, 1950–1966 (Arthritic scale).
SOURCE: National Center for Chronic Disease Control.

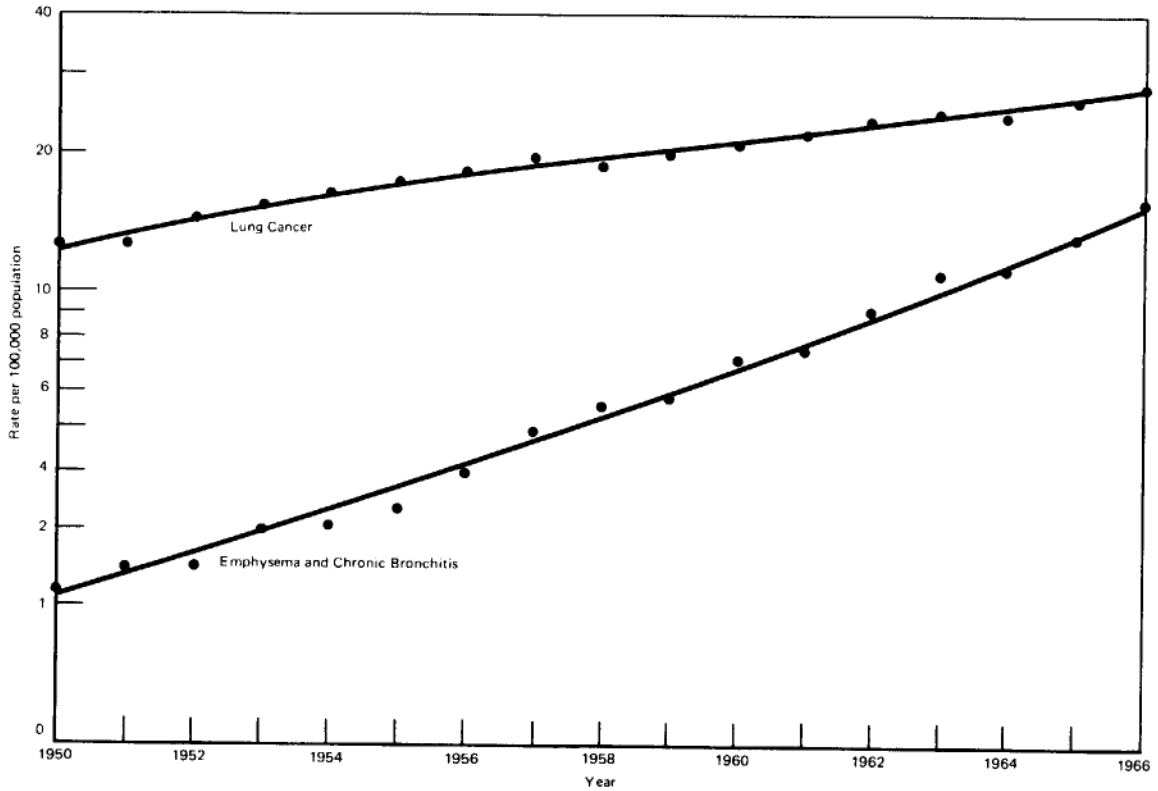

FIGURE 2—Death rates for emphysema and chronic bronchitis and for lung cancer: United States, 1950–1966 (Logarithmic scale).
SOURCE: National Center for Chronic Disease Control.

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 $FEV_{.75}$ 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 ciliatoxic 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 direcly 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 ciliatoxic 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 ciliatoxic 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_1.

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 bronchitics 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 bronchropulmonary 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 bronchopumonary 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.

CITED REFERENCES

(*1*) Auerbach, O., Hammond, E. C., Garfinkel, L. Thickening of walls of arterioles and small arteries in relation to age and smoking habits. New England Journal of Medicine 278(18): 980–984. May 2, 1968.

(*2*) Aviado, D. M., Palecek, F. Pulmonary effects of tobacco and related substances. I. Pulmonary compliance and resistance in the anesthetized dog. Archives of Environmental Health 15(2): 187–193. August 1967.

(*3*) Aviado, D. M., Samanek, M. Bronchopulmonary effects of tobacco and related substances. I. Bronchoconstriction and bronchodilatation: In-

fluence of lung denervation. Archives of Environmental Health 11(2): 141–151, August 1965.

(4) AVIADO, D. M., SAMANEK, M., FOLLE, L.E. Cardiopulmonary effects of tobacco and related substances. I. The release of histamine during inhalation of cigarette smoke and anoxemia in the heart-lung and intact dog preparation. Archives of Environmental Health 12(6): 705–724, June 1966.

(5) BATES, D. V. Chronic bronchitis and emphysema. New England Journal of Medicine 278(10): 546–551, March 7, 1968.

(6) BATES, D. V. Chronic bronchitis and emphysema (concluded). New England Journal of Medicine 278(11): 600–605, March 14, 1968.

(7) BOUHUYS, A., GEORG, J., JONSSON, R., LUNDIN, G., LINDELL, S. E., The influence of histamine inhalation on the pulmonary diffusing capacity in man. Journal of Physiology 152: 176–181, June 1960.

(8) BOUHUYS, A., JONSSON, R., LIGHTNECKERT, S., LINDELL, S. E., LUNDGREEN, C., LUNDIN, G., RINGQUIST, T. R., Effects of histamine on pulmonary ventilation in man. Clinical Science 19: 79–94, February 1960.

(9) BURROWS, B., NIDEN, A. H., FLETCHER, C. M., JONES, N. L. Clinical types of chronic obstructive lung disease in London and in Chicago. A study of one hundred patients. American Review of Respiratory Diseases 90(1): 14–27, July 1964.

(10) DALHAMN, T., ROSENGREN, A. The effect of oxygen lack on the tracheal ciliary activity. Archives of Environmental Health 16(3): 371–373, March 1968.

(11) DALHAMN, T., RYLANDER, R. Tar content and ciliotoxicity of cigarette smoke. Acta Pharmacologica et Toxicologica 25(3): 369–372, 1967.

(12) DALHAMN, T., RYLANDER, R., SPEARS, A. W. Differences in ciliotoxicity of cigarette smoke. American Review of Respiratory Diseases 96(5): 1078–1079, November 1967.

(13) DAVIS, T. R. A., BATTISTA, S. P., KENSLER, C. J. Mechanism of respiratory effects during exposure of guinea pigs to irritants. Archives of Environmental Health 15(4): 412–419, October 1967.

(14) EDELMAN, N. H., MITTMAN, C., NORRIS, A. H., COHEN, B. H., SHOCK, N. W. The effects of cigarette smoking upon spirometric performance of community dwelling men. American Review of Respiratory Diseases 94(3): 421–429, September 1966.

(15) FERIN, J. The mechanism of elimination of deposited particles from the lungs. (Report of meeting.) Annals of Occupational Hygiene 10(3): 207–216, July 1967.

(16) FILLEY, G. F., BECKWITT, H. J., REEVES, J. T., MITCHELL, R. S. Chronic obstructive bronchopulmonary disease. II. Oxygen transport in two clinical types. American Journal of Medicine 44(1): 26–38, January 1968.

(17) FLETCHER, C. M. Bronchial infection and reactivity in chronic bronchitis. Journal of the Royal College of Physicians of London 2(2): 183–190, January 1968.

(18) FLETCHER, C. M., HUGH-JONES, P., MCNICOL, M. W., PRIDE, N. B. The diagnosis of pulmonary emphysema in the presence of chronic bronchitis. Quarterly Journal of Medicine 32: 33–44, January 1963.

(19) FOLLE, L. E., SAMANEK, M., AVIADO, D. M. Cardiopulmonary effects of tobacco and related substances. II. Coronary vascular effects of cigarette smoke and nicotine. Archives of Environmental Health 12(6): 712–716, June 1966.

(20) FORGACS, J., CARLL, W. T. Mycotoxicoses: Toxic fungi in tobaccos. Science 152(3729): 1634–1635, June 17, 1966.

(21) Freour, P., Coudray, P., Roussel, A., Serise, A. Les bronchites chroniques et l'insuffisance respiratorie dans l'agglomeration de Bordeaux. Journal de Medecine de Bordeaux 143(2) : 1865–1879, December 1966.

(22) Giammona, S. T. Effects of cigarette smoke and plant smoke on pulmonary surfactant. American Review of Respiratory Diseases 96(3) : 539–541, September 1967.

(23) Guillerm, R., Saindelle, A., Faltot, P., Hee, J. Action de la fumee de cigarette et de quelques-uns de ses constituants dur les resistances ventilatoires chez le cobaye. Archives Internationales de Pharmacodynamie et de Therapie 167(1) : 101–114, May 1967.

(24) Haynes, W. F., Jr., Krstulovic, V. J., Bell, A. L. L., Jr. Smoking habit and incidence of respiratory tract infections in a group of adolescent males. American Review of Respiratory Diseases 93(5) : 730–735, May 1966.

(25) Higgins, I. T. T., Gilson, J. C., Ferris, B. G., Waters, E., Campbell, H. M., Higgins, M. W. Chronic respiratory diseases in an industrial town: A nine year follow-up study. [Unpublished.] Presented at the American Public Health Association Environmental Epidemiology Session, October 25, 1967. 18 pp.

(26) Holland, W. W., Elliott, A. Cigarette smoking, respiratory symptoms and anti-smoking propaganda. An experiment. Lancet 1(7532) : 41–43, January 6, 1968.

(27) Huhti, E. Ventilatory function in healthy non-smokers and smokers. Scandinavian Journal of Respiratory Diseases 48(2) : 149–155, 1967.

(28) Kaminski, E. J., Fancher, O. E., Calandra, J. C. *In vivo* studies of the ciliastatic effects of tobacco smoke. Absorption of ciliastatic components by wet surfaces. Archives of Environmental Health 16(2) : 188–193, February 1968.

(29) Kilburn, K. H., Salzano, J. V., editors. Symposium on structure, function, and measurement of respiratory cilia. Duke University Medical Center, Durham, N.C., February 18–19, 1965. American Review of Respiratory Diseases 93(3, Part 2) : 1–184, March 1966.

(30) Levine, B. E., Bigelow, D. B., Hamstra, R. D., Beckwitt, H. J., Mitchell, R. S., Nett, L. M., Stephen, T. A., Petty, T. L. The role of long-term continuous oxygen administration in patients with chronic airway obstruction with hypoxemia. Annals of Internal Medicine 66(4) : 641–650, April 1967.

(31) Lowe, C. R. Chronic bronchitis and occupation. Joint meeting No. 1. Section of Occupational Medicine with Section of Epidemiology and Preventive Medicine. Chronic Bronchitis and Occupation. Proceedings of the Royal Society of Medicine 61(1) : 98–102, January 1968.

(32) Lowe, C. R., Pelmear, P. L., Campbell, H., Hitchens, R. A. N., Khosla, T., King, T. C. Bronchitis in two integrated steel works. I. Ventilatory capacity, age, and physique of non-bronchitic men. British Journal of Preventive and Social Medicine 22(1) : 1–11, January 1968.

(33) Lucas, G. B. Diseases of Tobacco. New York, Scarecrow Press, 1965. 778 pp.

(34) Megahed, G. E., Senna, G. A., Eissa, M. H., Saleh, S. Z., Eissa, H. A. Smoking versus infection as the aetiology of bronchial mucous gland hypertrophy in chronic bronchitis. Thorax (London) 22(3) : 271–278, May 1967.

(35) Mitchell, R. S., Vincent, T. N., Ryan, S., Filley, G. F. Chronic obstructive broncho-pulmonary disease: IV. The Clinical and physiological differentiation of chronic bronchitis and emphysema. American Journal of the Medical Sciences 247 : 513–521, May 1964.

(36) NADEL, J. A., COMROE, J. H., JR. Acute effects of inhalation of cigarette smoke on airway conductance. Journal of Applied Physiology 16(4): 713–716, 1961.

(37) NASH, E. S., BRISCOE, W. A., COURNAND, A. The relationship between clinical and physiological findings in chronic obstructive disease of lungs. Medicina Thoracalis 22: 305–327, 1965.

(38) PALECEK, F., AVIADO, D. M. Pulmonary effects of tobacco and related substances. II. Comparative effects of cigarette smoke, nicotine, and histamine on the anesthetized cat. Archives of Environmental Health 15 (2): 194–203, August 1967.

(39) PALECEK, F., OSKOUI, M., AVIADO, D. M. Pulmonary effects of tobacco and related substances. III. Inhibition of synthesis of histamine in various species. Archives of Environmental Health 15(2): 204–213, August 1967.

(40) PENMAN, R. W. B., HOWARD, P. Distribution of pulmonary ventilation and blood flow in normal subjects and patients with chronic bronchitis. Clinical Science 30: 63–78, 1966.

(41) PENMAN, R. W. B., HOWARD, P., STENTIFORD, N. H. Factors influencing pulmonary gas exchange in patients with acute edematous cor pulmonale due to chronic lung disease. American Journal of Medicine 44(1): 8–15, January 1968.

(42) PETERSON, D. I., LONERGAN, L. H., HARDINGE, M. G. Smoking and pulmonary function. Archives of Environmental Health 16(2): 215–218, February 1968.

(43) PLATTS, M. M., HAMMOND, J. D. S., STUART-HARRIS, C. H. A study of cor pulmonale in patients with chronic bronchitis. Quarterly Journal of Medicine 29(116): 559–574, October 1960.

(44) RYLANDER, R. Pulmonary defence mechanisms to airborne bacteria. Acta Physiologica Scandinavica (Supplementum 306): 1–89, 1968.

(45) SAMANEK, M., AVIADO, D. M. Bronchopulmonary effects of tobacco and related substances. II. Bronchial arterial injections of nicotine and histamine. Archives of Environmental Health 11(2): 152–159, August 1965.

(46) SAMANEK, M., AVIADO, D. M. Bronchopulmonary effects of tobacco and related substances. IV. Bronchial vascular and broncho-motor responses; their suggested defense function. Archives of Environmental Health 11 (2): 167–176, August 1965.

(47) SAMANEK, M., AVIADO, D. M. Cardiopulmonary effects of tobacco and related substances. III. Pulmonary vascular effects of cigarette smoke and nicotine. Archives of Environmental Health 12: 717–724, June 1966.

(48) SAMANEK, M., AVIADO, D. M., PESKIN, G. W. Bronchopulmonary effects of tobacco and related substances. III. Axon reflexes elicited from the visceral pleura. Archives of Environmental Health 11(2): 160–166, August 1965.

(49) SEKULIC, S. M., HAMLIN, J. T., III, ELLISON, R. G., ELLISON, L. T. Evaluation of five methods for the study of pulmonary surfactant. American review of Respiratory Diseases 97(1): 131–135, January 1968.

(50) SEKULIC, S. M., HAMLIN, J. T., III, ELLISON, R. G., ELLISON, L. T. Pulmonary surfactant and lung circulation in experimental atelectasis. American Review of Respiratory Diseases 97(1): 69–75, January 1968.

(51) SIMONSSON, B. G. Clinical and physiological studies on chronic bronchitis. III. Bronchial reactivity to inhaled acetylcholine. Acta Allergologica 20(5): 325–348, 1965.

(52) SIMONSSON, B. G., JACOBS, F. M., NADEL, J. A. Role of autonomic nervous system and the cough reflex in the increased responsiveness of airways

in patients with obstructive airway disease. Journal of Clinical Investigation 46(11) : 1812–1818, 1967.

(53) SPURGASH, A., EHRLICH, R., PETZOLD, R. Effect of cigarette smoke on resistance to respiratory infection. Archives of Environmental Health 16 (3) : 385–391, March 1968.

(54) STANEK, V., FODOR, J., HEJL, Z., WIDIMSKY, J., CHARVAT, P., SANTRUCEK, M., ZAJIC, F., VAVRIK, M. A contribution to the epidemiology of chronic bronchitis. Acta Medica Scandinavica 179(6) : 737–746, June 1966.

(55) STRIEDER, D. J., KAKEMI, H. Hypoxemia in young asymptomatic cigarette smokers. Annals of Thoracic Surgery 4(6) : 523–531, December 1967.

(56) STUART-HARRIS, C. H. Pulmonary hypertension and chronic obstructive bronchitis. American Review of Respiratory Diseases 97(1) : 9–17, January 1968.

(57) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Public Health Service Review : 1967. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1967. 227 pp.

(58) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEALTH STATISTICS. Mortality from diseases associated with smoking: United States, 1950–64. Washington, U.S. Department of Health, Education, and Welfare, Vital and Health Statistics, Series 20, No. 4, Public Health Service Publication No. 1000, October 1966. 45 pp.

(59) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service, Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.

(60) WILHELMSEN, L. Effects on bronchopulmonary symptoms, ventilation, and lung mechanics of abstinence from tobacco smoking. Scandinavian Journal of Respiratory Diseases 48(3/4) : 407–414, 1967.

(61) WILLIAMS, J. B., ANDERSON, W. H. Acute effects of cigarette smoke on distribution of pulmonary perfusion. Clinical Research 16(2) : 377, April 1968.

(62) WYNDER, E. L., TAGUCHI, K. T., BADEN, V., HOFFMAN, D. Tobacco carcinogenesis. IX. Effect of cigarette smoke on respiratory tract of mice after passive inhalation. Cancer 21(1) : 134–153, January 1968.

(63) YEAGER, H., JR., RIVES, M. W., MASSARO, D. Personal communication. 1968.

SUPPLEMENTAL BRONCHOPULMONARY REFERENCES

S1. ADELSTEIN, A. M., RIMINGTON, J. Smoking and pulmonary tuberculosis: An analysis based on a study of volunteers for mass miniature radiography. Tubercle 48(3) : 219–226, September 1967.

S2. ALBERT, R. E., LIPPMANN, M., BRISCOE, W. The characteristics of bronchial clearance in humans and the effects of cigarette smoking. Presented at the annual meeting of the American Medical Association, June 19, 1968 in San Francisco, Calif.

S3. ANDERSON, D. O. The effects of air contamination on health: Part I. (Current progress.) Canadian Medical Association Journal 97(10) : 528–536, September 2, 1967.

S4. ANDERSON, D. O. The effects of air contamination on health: A review. Part II. (Current progress.) Canadian Medical Association Journal 97(11) : 3 585–593, September 9, 1967.

S5. ASHFORD, J. R., BROWN, S., MORGAN, D. C., RAE, S. The pulmonary ventilatory function of coal miners in the United Kingdom. American Review of Respiratory Diseases 97 : 810–826, 1968.

S6. AUERBACH, O., HAMMOND, E. C., KIRMAN, D., GARFINKEL, L., STOUT, A. P. Histologic changes in bronchial tubes of cigarette-smoking dogs. Cancer 20(12): 2055–2066, December 1967.

S7. BARER, G. R., HOWARD, P., MCCURRIE, J. R. The effect of carbon dioxide and changes in blood pH on pulmonary vascular resistance in cats. Clinical Science 32: 361–376, 1967.

S8. BECKETT, A. H., ROWLAND, M., TRIGGS, E. J. Significance of smoking in investigations of urinary excretion rates of amines in man. Nature (London) 207 (4993): 200–201, July 10, 1965.

S9. BIEGEL, A. A., KRUMHOLZ, R. A. An immunoglobulin abnormality in pulmonary emphysema. American Review of Respiratory Diseases 97(2): 217–222, February 1968.

S10. BONOMO, L., D'ADDABBO, A. [131] Albumin turnover and the loss of protein into the sputum in chronic bronchitis. Clinica Chimica Acta 10: 214–222, 1964.

S11. BOREN, H. G., Pathobiology of air pollutants. Supported by U.S. Public Health Service Grant No. OH-00267, 1966. [Unpublished] 31 pp.

S12. BRISCOE, W. A., DUBOIS, A. B. The relationship between airway resistance, airway conductance and lung volume in subjects of different age and body size. Journal of Clinical Investigation 37: 1279–1285, 1958.

S13. BURROWS, B., FLETCHER, C. M., HEARD, B. E., JONES, N. L., WOOTLIFF, J. S. The emphysematous and bronchial types of chronic airway obstruction. A Clinicopathological study of patients in London and Chicago. Lancet 1(7442): 830–835, April 16, 1966.

S14. BURROWS, B., NIDEN, A. H., BARCLAY, W. R., KASIK, J. E. Chronic obstructive lung disease. II. Relationship of clinical and physiologic findings to the severity of airways obstruction. American Review of Respiratory Diseases 91(5): 665–678, May 1967.

S15. CANTER, H. G., LUCHSINGER, P. C. Interrelationships of smoking habits, race, and maximal terminal flow. American Review of Respiratory Diseases 96(1): 147–148, July 1967.

S16. CAREY, G. C. R., DAWSON, T. A. J., MERRETT, J. D. Daily changes in ventilatory capacity in smokers and in non-smokers. British Journal of Preventive and Social Medicine 21(2): 86–89, April 1967.

S17. COURANT, P. The effect of smoking on the antilactobacillus system in saliva. Odontologisk Revy (Malmo) 18: 251–261, 1967.

S18. DAWSON, A. Reproducibility of spirometric measurements in normal subjects. American Review of Respiratory Diseases 93(2): 264–268, February 1966.

S19. DE CLERCQ, M., TRUHAUT, R. Recherches sur le metalobisme du trytophane chez le rat soumis a l'intoxication chronique par la cotinine. Etude de l'elimination urinaire et dosage dans le cerveau et les intestins de certains derives indoliques. Bulletin de la Societe de Chimie Biologique 45(9/10): 995–1001, 1963.

S20. DENSEN, P. M., JONES, E. W., BASS, H. E., BREUER, J. A survey of respiratory disease among New York City postal and transit workers. 1. Prevalence of symptoms. Environmental Research 1: 262–286, 1967.

S21. DOUGLAS, J. W. B., WALLER, R. E. Air pollution and respiratory infection in children. British Journal of Preventive and Social Medicine 20(1): 1–8, January 1966.

S22. DUBOIS, A. B., BOTELHO, S. Y., COMROE, J. H., JR. A new method for measuring airway resistance in man using a body plethysmograph: Values in normal subjects and in patients with respiratory disease. Journal of Clinical Investigation 35: 327–335, 1956.

S23. FERIN, J. Pulmonary clearance after deposition of aerosols. Lekarske Prace 5(1) : 5–67, 1966.

S24. FODOR, J. T., GLASS, L. H., WEINER, J. M. The immediate effects of smoking on young healthy males. Presented at the Joint Session of the School Health Section, American Public Health Association and the American School Health Association, 95th Annual Meeting, Miami, Florida, October 26, 1967. [Unpublished.] 17 pp.

S25. GEORGADZE, G. E. KRASNYANAKAYA, P. N. Izmeneniye v dykhatel'nykh putyakh krolikov pri dlitel'nom vozdeystvii tabachnym dymom. Voprosy Onkologii 13(4) : 58–62, 1967.

S26. GIAMMONA, S. T., KERNER, D., BONDURANT, S. Effect of oxygen breathing at atmospheric pressure on pulmonary surfactant. Journal of Applied Physiology 20 : 855–858, 1965.

S27. GONZALEZ, E., WEILL, H., ZISKIND, M. M., GEORGE, R. B. The value of the single breath diffusing capacity in separating chronic bronchitis from pulmonary emphysema. Diseases of the Chest 53(3) : 229–236, March 1968.

S28. GOUGH, J. The pathology of emphysema. Postgraduate Medical Journal 41 : 392–400, July 1965.

S29. GREEN, G. M., CAROLIN, D. The depressant effect of cigarette smoke on the *in vitro* antibacterial activity of alveolar macrophages. The New England Journal of Medicine 276(8) : 421–427, February 23, 1967.

S30. GREGG, I. The identification of the early stages of chronic bronchitis. Medicina Thoracalis 24(1) : 77, 1967.

S31. GROSS, P., DETREVILLE, R. T. P., BABYAK, M. A., KASCHAK, M. TOLKER, E. B. Experimental emphysema. Effect of chronic nitrogen dioxide exposure and papain on normal and pneumoconiotic lungs. Archives of Environmental Health 16(1) : 51–58, January 1968.

S32. GUYATT, A. R., ALPERS, J. H. Factors affecting airways conductance: A study of 752 working men. Journal of Applied Physiology 24(3) : 310–316, March 1968.

S33. HACKETT, R. L., SUNDERMAN, F. W. Pulmonary alveolar reaction to nickel carbonyl. Ultrastructural and histochemical studies. Archives of Environmental Health 16(3) : 349–361, March 1968.

S34. HICKEN, P., HEATH, D., BREWER, D. B., WHITAKER, W. The small pulmonary arteries in emphysema. Journal of Pathology in Bacteriology 90 : 107–114, 1965.

S35. HIGGINS, I. T. T. Final report. Studies of mining and non-mining communities in Marion County, West Virginia. Under Contract PH 86–64–89. University of Pittsburgh, Pittsburgh, Pennsylvania, Graduate School of Public Health, May 1, 1967. [Unpublished] 104 pp.

S36. HOLLAND, W. W., REID, D. D. The urban factor in chronic bronchitis. Lancet 1 : 445–448, February 27, 1965.

S37. HYATT, R. E., WILCOX, R. E. Extrathoracic airway resistance in man. Journal of Applied Physiology 16 : 326–330, 1961.

S38. JOHANNSEN, Z., PREIBISZ, J. Bezposredni wplyw palenia papierosow na spirogram u zdrowych i chorych z rozedma pluc i przewleklym niezytem oskrazeli. Polskie Archiwum Medycyny Wewnetrznej 36(6) : 783–786, 1966.

S39. JONES, N. L., BURROWS, B., FLETCHER, C. M. Serial studies of 100 patients with chronic airway obstruction in London and Chicago. Thorax 22(4) : 327–335, July 1967.

S40. KISS, G. T. Pulmonary survey in the aged. Diseases of the Chest 49(3) : 305–308, March 1966.

S41. KUEPPERS, F., BEARN, A. G. A possible experimental approach to the association of hereditary alpha-1-Antitrypsin deficiency and pulmonary emphysema. Proceedings of the Society for Experimental Biology and Medicine 121: 1207–1209, 1966.

S42. LAWS, J. W., HEARD, B. E. Emphysema and the chest film. A retrospective radiological and pathological study. British Journal of Radiology 35(419): 750–761, November 1962.

S43. LECLAIR, R. A. Recovery of culturable tobacco mosaic virus from sputum and thoracentesis fluids obtained from cigarette smokers with a history of pulmonary disease. American Review of Respiratory Diseases 95(3): 510–511, March 1967.

S44. LINDALL, A., MEDINA, A., GRISMER, J. T. A re-evaluation of normal pulmonary function measurements in the adult female. (Notes) American Review of Respiratory Diseases 95(6): 1061–1064, June 1967.

S45. LUPU, N. G., VELICAN, C. Histochemistry of connective-tissue mucopolysaccharides and proteins after experimental inhalation of tobacco smoke. Federation Proceedings [Translation Supplement] 22(3, pt. 2): 497–501, May–June 1963.

S46. LUPU, N. G., VELICAN, C., RACOVEANU, C. Fibrosis pulmonar por tabaco. Prensa Medica Argentina 53(1a8): 646–651, 1966.

S47. LUPU, N. G., VELICAN, C., RACOVEANU, C. Sclerozele pulmonare. Bucharest, Rumania, 1960. 373 pp.

S48. LUPU, N. G., VELICAN, C., VELICAN, D. Nablyudeniya po povodu vnutrilegochnykh nakopleniy kislykh mukopolisakharidov. Arkiv Patologii (Moskva) 21(6): 51–59, 1959.

S49. MCCARROLL, J., CASSELL, E. J., WOLTER, D. W., MOUNTAIN, J. D., DIAMOND, J. R., MOUNTAIN, I. M. Health and the urban environment. V. Air pollution and illness in a normal urban population. Archives of Environmental Health 14(1): 178–183, January 1967.

S50. MCDERMOTT, M., COLLINS, M. M. Acute effects of smoking on lung airways resistance in normal and bronchitic subjects. Thorax 20: 562–569, 1965.

S51. MEDICAL RESEARCH COUNCIL. WORKING PARTY ON TRIALS OF CHEMOTHERAPY IN EARLY CHRONIC BRONCHITIS. Value of chemotherapy in early chronic bronchitis. British Medical Medical Journal 1: 1317–1322, May 28, 1966.

S52. MILLER, D., BONDURANT, S. Effects of cigarette smoke on the surface characteristics of lung extracts. American Review of Respiratory Diseases 85(5): 692–696, May 1962.

S53. MILLS, M., BAISCH, B. F. Spontaneous pneumothorax: A series of 400 cases. The Annals of Thoracic Surgery 1(3): 286–297, May 1965.

S54. MITCHELL, R. S., RYAN, S. F., PETTY, T. L., FILLEY, G. F. The significance of morphologic chronic hyperplastic bronchitis. American Review of Respiratory Diseases 93(5): 720–729, May 1966.

S55. NADEL, J. A., COMROE, J. H., Jr. Acute effects of inhalation of cigarette smoke on airway conductance. Journal of Applied Physiology 16(4): 713–716, 1961.

S56. NADEL, J. A., SALEM, H., TAMPLIN, B., TOKIWA, Y. Mechanism of bronchoconstriction during inhalation of sulfur dioxide. Journal of Applied Physiology 20: 164–167, 1965.

S57. NICKLAUS, T. M., STOWELL, D. W., CHRISTIANSEN, W. R., RENZETTI, A. D., Jr. The accuracy of the roentgenologic diagnosis of chronic pulmonary emphysema. American Review of Respiratory Diseases 93(6): 889–899, June 1966.

S58. NICOLAS, R. Klinisch-experimentelle Sputumuntersuchungen bei chronischer Bronchitis. Medicina Thoracalis 21: 223–255, 1964.

S59. PAIN, M. C. F., GLAZIER, J. B., SIMON, H., WEST, J. B. Regional and overall inequality of ventilation and blood flow in patients with chronic airflow obstruction. Thorax 22: 453–461, 1967.

S60. PAPADOPOULOS, N. Metabolism of nicotine in animal tissues *in vitro* and *in vivo*. In: Tobacco Alkaloids and Related Compounds. Proceedings of the 4th International Symposium, held at the Wenner-Gren Center, Stockholm, February 1964. Pp. 101–104.

S61. PARNELL, J. L., ANDERSON, D. O. KINNIS, C. Cigarette smoking and respiratory infections in a class of student nurses. New England Journal of Medicine 274(18): 979–984, May 5, 1966.

S62. PELZER, A. M., THOMSON, M. L. Effect of age, sex, stature, and smoking habits on human airway conductance. Journal of Applied Physiology 21(3): 469–476, March 1966.

S63. PEMBERTON, J. Occupational factors in chronic bronchitis. Joint Meeting No. 1. Section of Occupational Medicine with Section of Epidemiology and Preventive Medicine. Chronic Bronchitis and Occupation. Proceedings of the Royal Society of Medicine 61(1): 95–98, January 1968.

S64. RANKIN, J., GEE, J. B. L., CHOSY, L. W. The influence of age and smoking on pulmonary diffusing capacity in healthy subjects. Medicina Thoracalis 22: 366–374, 1965.

S65. REID, L. Mucous secretion and chronic bronchitis. Medicina Thoracalis 24: 40–43, 1967.

S66. REID, L., MILLARD, F. J. C. Correlation between radiological diagnosis and structural lung changes in emphysema. Clinical Radiology 15: 307–311, October 1964.

S67. ROSE, B., PHILLS, J. A. The immune reaction in pulmonary disease. Archives of Environmental Health 14(1): 97–110, January 1967.

S68. ROSS, C. A. C., MCMICHAEL, S., EADIE, M. B., LEES, A. W., MURRAY, E. A., PINKERTON, I. Infective agents and chronic bronchitis. Thorax 21: 461–464, 1966.

S69. ROSS, J. C., LEY, G. D., KRUMHOLZ, R. A., RAHBARI, H. A technique for evaluation of gas mixing in the lung: Studies in cigarette smokers and non-smokers. American Review of Respiratory Diseases 95(3): 447–453, March 1967.

S70. SENIOR, R. M., FISHMAN, A. P. Disturbances of alveolar ventilation. Medical Clinics of North America 51(2): 403–425, March 1967.

S71. SEVCIK, M. Vliv koureni na nemoci dychadel a bronchospasmus. Rozhledy v Tuberkulose a v Nemocech Plicnich 26(8): 571–575, 1966.

S72. SHIOTA, K., HAMADA, A., MAEDA, Y., OKA, Y., EMURA, M., MITANI, K., MATSUDA, M., INOUE, T., SAWAI, M., KAWAMURA, S., OKUBO, M. 11. Studies on chronic bronchitis in Osaka. Japanese Journal of Medicine 6(2): 105–106, April 1967.

S73. SIMON, G. Radiology and emphysema. Clinical Radiology 15: 293–306, October 1964.

S74. SIMONSSON, B. G. Clinical and physiological studies on chronic bronchitis. I. Clinical description of the patient material. Acta Allergologica 20(4): 257–300, 1965.

S75. SLUIS-CREMER, G. K., WALTERS, L. G., SICHEL, H. S. Chronic bronchitis in miners and non-miners: An epidemiological survey of a community in the gold-mining area in the Transvaal. British Journal of Industrial Medicine 24(1): 1–12, January 1967.

S76. SPIEGLEMAN, J. R., ALBERT, R. E., SHATSKY, S., LIPPMAN, M. The effect of acute exposure to cigarette smoke on bronchial clearance in the miniature donkey. Archives of Environmental Health: 1968. (In press.)

S77. STANESCU, D. C., PILAT, L., GAVRILESCU, N., TECULESCU, D. B., CRITESCU, I. Aspects of pulmonary mechanics in arc welders' siderosis. British Journal of Industrial Medicine 24(2) : 143–147, April 1967.

S78. STERLING, G. M. Mechanism of bronchoconstriction caused by cigarette smoking. British Medical Journal 3 : 275–277, July 29, 1967.

S79. STRIEDER, D. J., KAZEMI, H. Effect of body position on the alveolar-arterial P_{O_2} difference in smokers. Clinical Research 16(2) : 474, April 1968.

S80. STRIEDER, D. J., MURPHY, R., KAZEMI, H. Hypoxemia in asymptomatic smokers. Clinical Research 16(2) : 376, April 1968.

S81. SUKUMALCHANTRA, Y., WILLIAMS, M. H., Jr. Serial studies of pulmonary function in patients with chronic obstructive pulmonary disease. American Journal of Medicine 39(12) : 941–945, December 1965.

S82. SUTINEN, S., CHRISTOFORIDIS, A. J., KLUGH, G. A., PRATT, P. C. Roentgenologic criteria for the recognition of nonsymptomatic pulmonary emphysema : Correlation between roentgenologic findings and pulmonary pathology. American Review of Respiratory Diseases 91 : 69–76, 1965.

S83. TALAMO, R. C., BLENNERHASSETT, J. B., AUSTEN, K. F. Current concepts : Familial emphysema and Alpha$_1$-Antirypsin deficiency. New England Journal of Medicine 275(23) : 1301–1305, December 8, 1966.

S84. THURLBECK, W. M., ANGUS, G. E. The variation of Reid index measurements within the major bronchial tree. American Review of Respiratory Diseases 95(4) : 551–555, April 1967.

S85. TISI, G., WOLFE, W., FALLAT, R., NADEL, J. Role of O_2 and CO_2 in reversal of changes in mechanical properties of the lung following pulmonary vascular occlusion. Clinical Research 16(2) : 376, April 1968.

S86. TOMANEK, A., FISER, F. Bronchoskopicke nalezy u kuraku. Rozhledy v Tuberkulose a v Nemocech Plicnich 27(10) : 687–695, 1967.

S87. WALSHE, M. M., HAYES, J. A. Respiratory symptoms and smoking habits in Jamaica. American Review of Respiratory Diseases 96(4) : 640–644, October 1967.

S88. ZAMEL, N., YOUSSEF, H. H., PRIME, F. J. Airway resistance and peak expiratory flow-rate in smokers and non-smokers. Lancet 1(7293) : 1237–1238, June 8, 1963.

S89. ZEIDBERG, L. D., HORTON, R. J. M., LANDAU, E. The Nashville Air Pollution Study. V. Mortality from diseases of the respiratory system in relation to air pollution. Archives of Environmental Health 15(2) : 214–224, August 1967.

S90. ZWI, S., SLUIS-CREMER, G. K., DU PREEZ, L. A survey of pulmonary function in male office workers. Medical Proceedings 13(23) : 569–574, November 11, 1967.

CHAPTER 3

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. Aditional 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 bucal 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 carcinogensis. 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 (*39,83,88*).

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, commerical 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 occuring 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-cholorophenyl) 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 Negroni (*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 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 (*95*).

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. (*57*).

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 Guillan, 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 nonsmokers for both males and females. There is also a positive correlation between lung cancer death rates and both the amount smoked and the

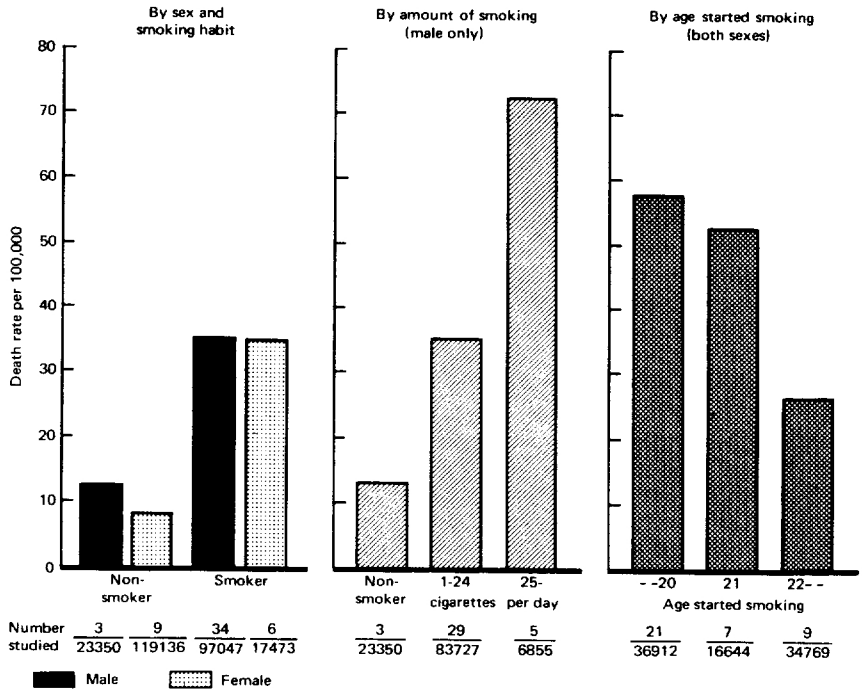

FIGURE 1—Death rates for lung cancer, among persons age over 40 years, classified by sex and extent of cigarette smoking, and by age smoking began: Study of 29 Health Center Districts in Japan, January 1966 to March 1967.

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 anlysis 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

*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.

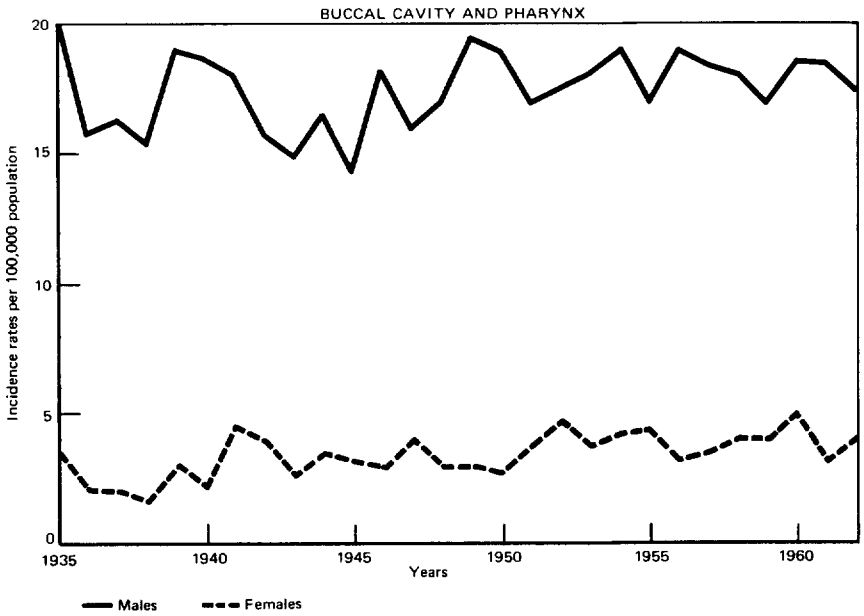

FIGURE 2—Age-adjusted rates of the incidence of cancer of the buccal cavity and pharynx, for males and females: Connecticut, 1935–1962.

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 alchohol 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.

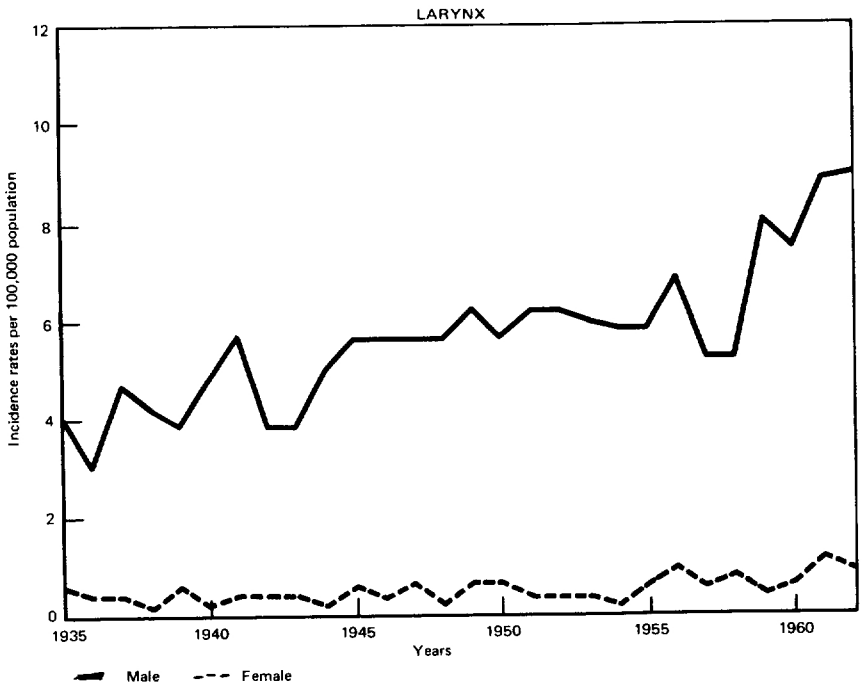

FIGURE 3—Age-adjusted rates of the incidence of cancer of the larynx, for males and females: Connecticut, 1935–1962

SOURCE: Eisenberg et al. (*24*).

The American Cancer Society (*2*) estimates the occurence 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.

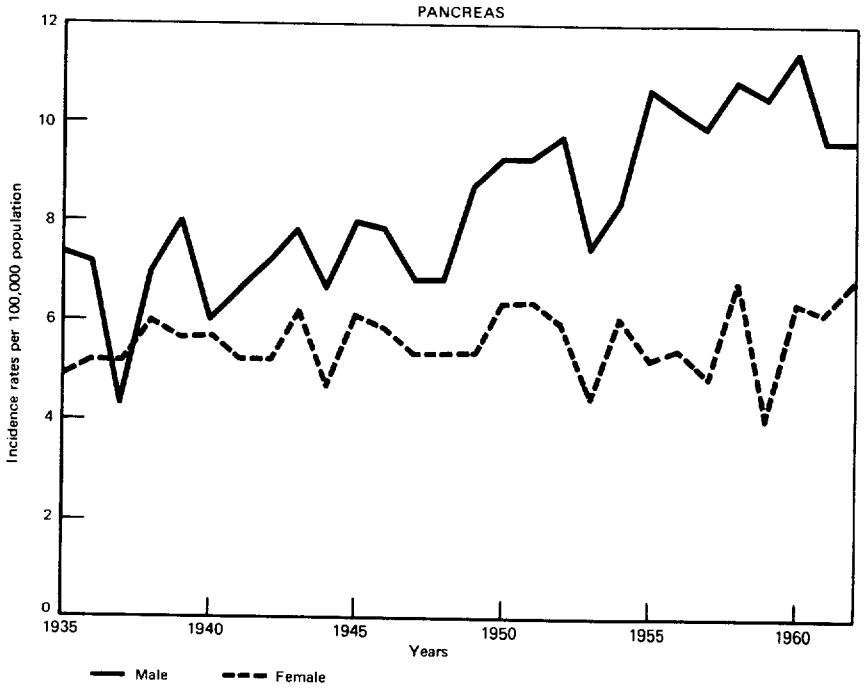

FIGURE 4—Age-adjusted rates of the incidence of cancer of the pancreas, for males and females: Connecticut, 1935–1962.

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

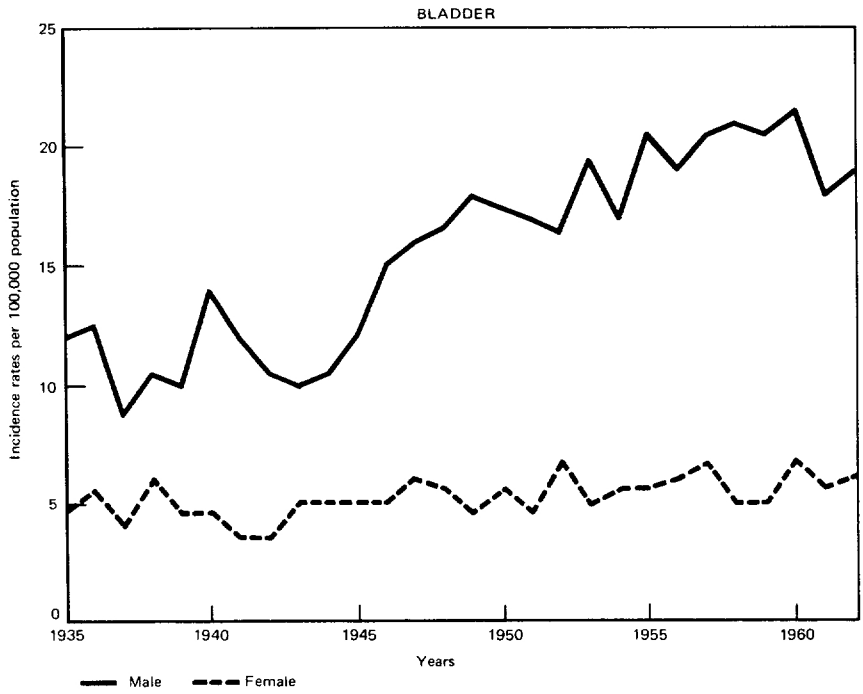

FIGURE 5—Age-adjusted rates of the incidence of cancer of the bladder, for males and females: Connecticut, 1935–1962.

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	[1] (4)6	[1] (15)23

[1] 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.

CITED REFERENCES

(*1*) ABELIN, T., GSELL, O. T. Relative risk of pulmonary cancer in cigar and pipe smokers. Cancer 20(8) : 1288–1296, August 1967.

(*2*) AMERICAN CANCER SOCIETY. 1968 Cancer facts and figures. New York, 1967. 31 pp.

(*3*) AUERBACH, O. Personal communication. March 1968.

(*4*) AUERBACH, O., HAMMOND, E. C., KIRMAN, D., GARFINKEL, L., STOUT, A. P. Histologic changes in bronchial tubes of cigarette-smoking dogs. Cancer 20(12) : 2055–2066, December 1967.

(*5*) BEST, E. W. R. A Canadian study of smoking and health. Ottawa, Department of National Health and Welfare, 1966. 137 pp.

(*6*) BOCK, F. G. Personal communication. April 1968.

(*7*) BOCK, F. G. Dose response: Experimental carcinogenesis. *In:* Wynder E. L., Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesa, U. S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press.)

(*8*) BRETTHAUER, E. W., BLACK, S. C. Polonium-210: Removal from smoke by resin filters. Science 156(3780) : 1375–1376, June 9, 1967.

(*9*) BROSS, I. D. J. Effort of filter cigarettes on the risk of lung cancer: *In:* Wynder, E. L., Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press.)

(*10*) BROWN, R. L., SUH, J. M., SCARBOROUGH, J. E., WILKINS, S. A., Jr., SMITH, R. R. Snuff dippers' intraoral cancer: Clinical characteristics and response to therapy. Cancer 18(1) : 2–13, January 1965.

(*11*) BUELL, P., DUNN, J. E. Relative impact of smoking and air pollution on lung cancer. Archives of Environmental Health 15(3) : 291–297, September 1967.

(*12*) BUELL, P., DUNN, J. E., BRESLOW, L. Cancer of the lung and Los Angeles-type air pollution. Prospective study. Cancer 20(12) : 2139–2147, December 1967.

(*13*) CARFI, N., DUGNANI-LONATI, R. Polonium-210 in Italian tobacco. Health Physics 12 : 1808, December 1966.

(*14*) CASARET, L. J. The role of radioactive substances in effects of smoking. *In:* Wynder, E. L., Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press.)

(*15*) COOPER, D. A., CRANE, A. R., BOUCOT, K. R. Primary carcinoma of the lung in nonsmokers. Archives of Environmental Health 16(3) : 398–400, March 1968.

(*16*) DEELEY, T. J., COHEN, S. L. The relationship between cancer of the bladder and smoking. *In:* Bladder Cancer. Chapter 13. Proceedings of the

5th Inter-American Conference on Toxicology and Occupational Medicine, University of Miami, School of Medicine, Coral Gables, Fla., 1966. Pp. 163–169.

(17) DICKENS, F. Mold products, including antibiotics as carcinogens. *In:* Carcinogenesis: A broad critique. Houston, The University of Texas, M. D. Anderson Hospital, 1967. Pp. 447–470.

(18) DOLL, R., HILL, A. B. Mortality in relation to smoking: Ten years' observations of British doctors. British Medical Journal 1(5395): 1399-1410, May 30, 1964.

(19) DOLL, R., HILL, A. B. Mortality in relation to smoking: Ten years' observations of British doctors. British Medical Journal 1(5396): 1460-1467, June 6, 1964.

(20) DONTENWILL, W., RECKZEH, G., STADLER, L. Inhalationsexperimente mit Cigareetenrauch. Beiträge zur Tabakforschung 3(6): 438–448, September 1966.

(21) DUNGAL, N. Lung carcinoma in Iceland. Lancet 2(6624): 245–247, August 12, 1950.

(22) DUNN, W. I., DYKSTRA, C. L. Tobacco habits in carcinoma of the upper respiratory tract. Archives of Otolaryngology 86(1): 79-81, July 1967.

(23) DYMOND, H. F., KILHORN, K. D. The characterization of tobacco smoke by gas chromatography and a digital computer. *In:* Littlewood, A. B., editor. Gas Chromatography 1966. London, The Institute of Petroleum, 1967. Pp. 353–392.

(24) EISENBERG, H., CAMPBELL, P. C., FLANNERY, J. T. Cancer in Connecticut. Incidence characteristics 1935-1962. Hartford, Connecticut State Department of Health, 1967. 97 pp.

(25) EPSTEIN, S. S., ANDREA, J., JAFFEE, H., JOSHI, S., FALK, H., MANTEL, N. Carcinogenicity of the herbicide *maleic hydrazide*. Nature (London) 215(5108): 1388–1390, Sept. 23, 1967.

(26) ERMOLAEVA-MAKOVASAYA, A. P., PERTOSOV, L. A., POPOV, D. K. Polonium-210 content of tobacco. Gigiena i Sanitariya 30: 40–43, December 1965.

(27) FERRI, E. S., BARATTA, E. J. Polonium-210 in tobacco products and human tissues. Radiological Health Data and Reports 7(9): 485–488, September 1966.

(28) FERRI, E. S., CHRISTIANSEN, H. Lead-210 in tobacco cigarette smoke. Public Health Reports 83(9): 828–832, September 1967.

(29) FROST, D. V. Selenium and cancer. Chemical and Engineering News 45(44): 6, October 16, 1967.

(30) GRAHAM, S. Cancer of the lung related to smoking behavior. Cancer 21 (3): 523–530, March 1968.

(31) GUILLAN, R. A., ZELMAN, S., ALONSO, R. A. Adenocarcinoma of the lungs. An analysis of 24 cases in men. American Journal of Clinical Pathology 47(5): 580–584, May 1967.

(32) GUTHRIE, E. F., BOWERY, T. G. Pesticide residues in tobacco. Residue Review 19: 31–56, 1966.

(33) HAENSZEL, W., SHIMKIN, M. B., MILLER, H. P. Tobacco smoking patterns in the United States. Public Health Monograph No. 45, May 1956. 111 pp.

(34) HAMMOND, E. C. Smoking in relation to the death rates of 1 million men and women. *In:* Haenszel, W., editor. Epidemiological Approaches to the Study of Cancer and Other Diseases. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966. Pp. 127–204.

(35) HARRIS, R. J. C., NEGRONI, G. Production of lung carcinomas in C57BL mice exposed to a cigarette smoke and air mixture. British Medical Journal 4(5580) : 637–641, Dec. 16, 1967.

(36) HIRAYAMA, T. An epidemiological study of oral and pharyngeal cancer in Central and Southeast Asia. Bulletin of the World Health Organization 34(1) : 41–69, 1966.

(37) HIRAYAMA, T. Smoking in relation to the death rates of 265,118 men and women in Japan. Tokyo, National Cancer Center, Research Institute, Epidemiology Division, September 1967. 14 pp.

(38) HOFFMANN, D., RATHKAMP, G. Chemical studies on Tobacco smoke. V. Quantitative determination of chlorinated hydrocarbon insecticides in cigarette tobacco and its smoke. Beiträge zur Tabakforschung: 1968. (In press.)

(39) HOFFMANN, D., WYNDER, E. L. Selective reduction of the tumorigenicity of tobacco smoke. Experimental approaches. *In:* Wynder, E. L., Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press.)

(40) HOLTZMAN, R. B. Polonium-210 in bronchial epithelium of cigarette smokers. (Letter) Science 155(3762) : 607, Feb. 3, 1967.

(41) HOLTZMAN, R. B., ILCEWICZ, F. H., Lead-210 and polonium-210 in tissues of cigarette smokers. Science 153(3741) : 1259–1260, Sept. 6, 1966.

(42) ISHIKAWA, S. Japan Lung Cancer Society epidemiological study on lung cancer, with special reference to the association with smoking habit. Tokyo, Japan. 7 pp.

(43) ISHII, K., HIRAYAMA, T. Personal communication. March 1968.

(44) JACOBI, U. Die natürliche Strahleneinwirkung auf den Atemtrakt. Biophysik 2 : 282–300, 1965.

(45) JOHNSON, D. E., MILLAR, J. D., RHOADES, J. W. Nitrosamines in tobacco smoke : *In:* Wynder, E. L., Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press.)

(46) KAHN, H. A. The Dorn Study of smoking and mortality among U.S. veterans : Report on 8½ years of observation. *In:* Haenszel, W., editor. Epidemiological Approaches to the Study of Cancer and Other Diseases. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966. Pp. 1–125.

(47) KELLER, A. Z. Personal communication. June 1968.

(48) KELLER, A. Z. Cirrhosis of the liver, alcoholism and heavy smoking associated with cancer of the mouth and pharynx. Cancer 20(6) : 1015–1022, June 1967.

(49) KELLER, A. Z. The epidemiology of lip, oral, and pharyngeal cancers, and the association with selected systemic diseases. American Journal of Public Health and the Nation's Health 53(8) : 1214–1228, August 1963.

(50) KELLER, A. Z., TERRIS, M. The association of alcohol and tobacco with cancer of the mouth and pharynx. American Journal of Public Health and the Nation's Health 55(10) : 1578–1585, October 1965.

(51) KILIBARDA, M., PETROVIC, D., PANOV, D., DJURIC, D. Contamination with polonium-210, uranium and radium-226 due to smoking. Health Physics 12 : 1808, December 1966.

(52) KOLB, W., BAUMGARTEL, K., DRESCHHOFF, G. Der Polonium-210 Gehalt von Rauchkondensat und Tabak. Umweltradioaktivitat und Strahlenbelastung No. 3 : 165–170, Dec. 6, 1966.

(53) KRAUS, F. T., PEREZ-MESA, C. Verrucous carcinoma. Clinical and pathologic study of 105 cases involving oral cavity, larynx and genitalia. Cancer 19(1) : 26–38, January 1966.

(54) KRISHNA, G., SAXENA, O. N., SINGH, A. K. Oral carcinoma. Indian Journal of Surgery 29(5) : 229–235, May 1967.

(55) KRÖLLER, E. Untersuchungen zum Nachweis von Nitrosaminen in Tabakrauch und Lebensmitteln. Deutsche Lebensmittel-Rundschau 63(10) : 303–305, October 1967.

(56) LACASSAGNE, A. Tumeurs des Cellules de Leydig du Testicule du Rat, sous l'influence de 162 l'o, p'-DDD. Unio Internationalis Contra Cancrum. Monograph No. 7 : 241–242, 1967.

(57) LITTLE, J. B., RADFORD, E. P., Jr. Polonium-210 in bronchial epithelium of cigarette smokers. (Letter) Science 155(3762) : 606–607, Feb. 3, 1967.

(58) MAGEE, P. N., BARNES, J. M. Carcinogenic nitroso compounds. Advances in Cancer Research 10 : 163–246, 1967.

(59) MASUDA, Y., MORI, K., KURATSUNE, M. Studies on bladder carcinogens in the human environment. I. Naphthylamines produced by prolysis of aminoacids. International Journal of Cancer 2(5) : 489–493, 1967.

(60) MILLER, R. L., STEDMAN, R. L. Essential absence of beta-nephthylamine in cigarette smoke condensate. Tobacco 165(8) : 32 Aug. 25, 1967.

(61) MITCHELL, R. I., GIESEKE, J. A. Mechanical filtration : A review of filtration mechanisms pertinent to cigarette smoke. *In:* Wynder, E. L., Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press.)

(62) MOORE, C. Multiple mouth-throat cancer. American Journal of Surgery 110(4) : 534–536, October 1965.

(63) MOORE, G. E., BOCK, F. G. "Tar" and nicotine levels of American cigarettes. *In:* Wynder, E. L., Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press.)

(64) MOSHY, R. J., HALTER, H. M. Reconstituted tobacco leaf technology : A tool for tobacco smoke modification. *In:* Wynder, E. L., Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press.)

(65) NEURATH, G. Tobacco products and smoke. General report. Beitrage zur Tabakforschung 4(1) : 1–17, August 1967.

(66) NEURATH, G. Zur Frage des Vorkommens von N-nitroso-Verbindungen in Tabakrauch. Experientia 23(5) : 400–404, 1967.

(67) PAILER, M., HÜBSCH, W. J., KUHN, H. Untersuchung der aliphatischen und aromatischen primaren und sekundären Amine des Zigarettenrauches mit Hilfe der Gaschromatographie und Massenspektrometrie. Fachliche Mitteilungen der Oesterreichischen Tabakregie No. 7 : 109–118, April 1967.

(68) RAJEWSKY, B., STAHLOHOFEN, W. Polonium-210 activity in the lungs of cigarette smokers. Nature 209(5030) : 1312–1313, Mar. 26, 1966.

(69) REDDY, D. G., ANGULI, V. C. Experimental production of cancer with betel nut, tobacco and slaked lime mixture. Journal of the Indian Medical Association 49(7) : 315–318, Oct. 1, 1967.

(70) RICHARDS, J. C., WOENS, W. F., Jr. Effect of porous cigarette papers on the yield of major vapor phase and certain particulate phase components of cigarette smoke. 20th Tobacco Chemists' Research Conference, Winston-Salem, N.C., Nov. 2, 1966. 16 pp.

(71) ROSENFELD, L., CALLAWAY, J. Snuff dipper's cancer. American Journal of Surgery 106(5) : 840–844, November 1963.

(72) ROSENFELD, L., CALLAWAY, J. Squamous cell carcinoma of the oral cavity. Southern Medical Journal 56(12) : 1394–1399, December 1963.

(73) ROTH, D., FREDERICKSON, D. T., OPPENHEIM, A., LONDON, M. Bioassay of the effects of smoking on DNA content of human respiratory epithelium. Cancer 21(6) : 1132–1136, June 1968.

(74) ROTH, D., OPPENHEIM, A., FREDERICKSON, D. T. DNA dependent dye binding by oral epithelium in relation to smoking habits. Archives of Environmental Health: 1968. (In press)

(75) ROZENBILDS, J. G. Carcinoma of the larynx and hypopharynx in South Australia 1952–1966. Medical Journal of Australia 2(6) : 244–249, Aug. 5, 1967.

(76) SERFONTEIN, W. J., SMIT, J. H. Evidence for the occurrence of N-nitrosamines in tobacco. Nature (London) 214(5084) : 169–170, Apr. 8, 1967.

(77) SHANTA, V., KRISHNAMURTHI, S. Further studies in etiology of carcinomas of the upper alimentary tract. Acta; Unio Internationalis contra Cancrum 20: 586–594, 1964.

(78) SHANTA, V., KRISHNAMURTHI, S. Further studies in aetiology of carcinomas of the upper alimentary tract. British Journal of Cancer 17(1) : 8–23, March 1963.

(79) SINGH, A. D., VON ESSEN, C. F. Buccal mucosa cancer in South India. Etiologic and clinical aspects. American Journal of Roentgenology, Radium Therapy and Nuclear Medicine 96(1) : 6–14, January 1966.

(80) SMITH, G. A. L., SULLIVAN, P. J., IRVINE, W. J. The determination of oxidisable nitrogen oxides present in cigarette smoke. Analyst 92: 456–462, July 1967.

(81) STECKER, R. H., DEVINE, K. D., HARRISON, E. G., Jr. Verrucose "snuff dipper's" carcinoma of the oral cavity. A case of self-induced carcinogenesis. Journal of the American Medical Association 189(11) : 838–840, Sept. 14, 1964.

(82) STEDMAN, R. L. The chemical composition of tobacco and tobacco smoke. Chemical Reviews 68(2) : 153–207, April 1968.

(83) STEDMAN, R. L. Nicotine reduction in tobacco and tobacco smoke. *In:* Wynder, E. L. Hoffman, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press)

(84) STOCKS, P. Lung cancer and bronchitis in relation to cigarette smoking and fuel consumption in twenty countries. British Journal of Preventive and Social Medicine 21(4) : 181–185, October 1967.

(85) STOCKS, P. Recent epidemiological studies of lung cancer mortality, cigarette smoking and air pollution, with discussion of a new hypothesis of causation. British Journal of Cancer 20(4) : 595–623, December 1966.

(86) TERRACOL, J., CALVET, J., MARQUES, P., COLL, J. Le tabac et le cancer du larynx. Vie Medicale 48: 1149–1150, August 1967.

(87) THORARINSSON, H., HALLBRIMSSON, J., BJARNASON, O., PETERSON, G., Carcinoma of the lung in Iceland. Diseases of the Chest 52(6) : 754–759, December 1967.

(88) TSO, T. C. The effect of farm production practices on nicotine and total particulate matter in cigarette smoke. *In:* Wynder, E. L., Hoffman, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press.)

(89) Tso, T. C., Harley, N., Alexander, L. T. Source of lead-210 and polonium-210 in tobacco. Science 153(3738) : 880–882, August 19, 1966.

(90) Tso, T. C., Sorokin, T. Examination of aflatoxin B_1 in leaf tobacco and in cigarette smoke condensate. Beiträge zur Tabakforschung 4(1) : 18–20, August 1967.

(91) U.S. Public Health Service. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.

(92) U.S. Public Health Service. The Health Consequences of Smoking. A Public Health Service Review : 1967. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1967. 227 pp.

(93) U.S. Public Health Service. National Clearinghouse for Smoking and Health. 1966 National Health Survey. [Unpublished data.]

(94) U.S. Public Health Service. National Center for Health Statistics. Mortality from diseases associated with smoking : United States, 1950–64. Washington, U.S. Department of Health, Education, and Welfare, Vital and Health Statistics Series 20, No. 4, Public Health Service Publication No. 1000, October 1966. 45 pp.

(95) U.S. Public Health Service, National Center for Health Statistics. Vital Statistics of the United States 1965 Mortality 2 (Part A) : 1967.

(96) U.S. Senate. Consumer Subcommittee. Reviewing progress made toward the development and marketing of a less hazardous cigarette. Hearings before the Consumer Subcommittee of the Committee on Commerce. U.S. Senate, 90th Congress, First Session, Aug. 23–25, 1967. Serial No. 90–52, 1968. 329 pp.

(97) Vincent, R. G., Marchetta, F. The relationship of the use of tobacco and alcohol to cancer of the oral cavity, pharynx or larynx. American Journal of Surgery 106(3) : 501–505. September 1963.

(98) Wahi, P. N., Kehar, U., Lahiri, B. Factors influencing oral and oropharyngeal cancers in India. British Journal of Cancer 19(4) : 642–660, December 1965.

(99) Waingrow, S. M., Horn, D., Ikard, F. F. Dosage patterns of cigarette smoking in American adults. American Journal of Public Health and the Nation's Health 58(1) : 54–70, January 1968.

(100) West, P. W. Selenium and cancer (reply to Dr. Frost) (letter). Chemical and Engineering News 45(44) : 6–7, Oct. 16, 1967.

(101) West, P. W. Selenium in paper and its possible association with lung cancer among cigarette smokers. [Unpublished.] 7 pp.

(102) Wynder, E. L. Personal Communication. March 1968.

(103) Wynder, E. L., Berg, J. W. Cancer of the lung among nonsmokers. Special reference to histologic patterns. Cancer 20(7) : 1161–1172, July 1967.

(104) Wynder, E. L., Hoffmann, D. Tobacco and tobacco smoke. Studies in experimental carcinogenesis. New York, Academic Press, 1967. 730 pp.

(105) Wynder, E. L., Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press)

(106) Wynder, E. L., Taguchi, K. T., Baden, V., Hoffmann, D. Tobacco carcinogenesis. IX. Effect of cigarette smoke on respiratory tract of mice after passive inhalation. Cancer 21(1) : 134–153, January 1968.

SUPPLEMENTAL CANCER REFERENCES

S1. ALLEN, M. S., Jr., DRASH, E. C. Primary melanoma of the lung. Cancer 21(1) : 154–159, January 1968.

S2. ASHLEY, D. J. B. Lung cancer in miners. Thorax 23(1) : 87–91, January 1968.

S3. AYRE, J. E., RESSEL, F. A. Early diagnosis of lung cancer by cytology. Medical Times 96(1) : 1–18, January 1968.

S4. BAKER, R. R., CHERRY, J. Carcinoma of the larynx. Archives of Surgery 90(3) : 449–453, March 1965.

S5. BEARD. R. E. (Discussion of) BENJAMIN, B. Actuarial methods of mortality analysis; adaptation to changes in the age and cause pattern. Proceedings of the Royal Society; Series B. Biological Sciences 159(974) : 56–64, Dec. 10, 1963.

S6. BLATT, I. M., HAWDOL, C. J. New concepts in management of head and neck cancer: Malignancy of floor of the mouth and tongue. Journal of the Louisiana State Medical Society 118(2) : 46–52, February 1966.

S7. BROSS, I. D. J. Spurious effects from an extraneous variable. Journal of Chronic Diseases 19 : 637–647, 1966.

S8. BROWN, J. R., SHEPARD, R. J. Some measurements of fitness in older female employees of a Toronto Department store. Canadian Medical Association Journal 97 : 1208–1213, Nov. 11, 1967.

S9. BROWN, P. W., FOWLER, C. A. The toxicity of tobacco smoke solutions to Proteus Vulgaris. Beitrage zur Tabakforschung 4(2) : 78–83, October 1967.

S10. BURDETTE, W. J., EVANS, C. Management of coin lesions and carcinoma of the lung. Annals of Surgery 161(5) : 649–673, May 1965.

S11. CARNOW, B. W. Bronchogenic carcinoma : A simple cytological office screening procedure for early detection. Chicago Medical School Quarterly 26 : 13–17, Spring 1966.

S12. CEDERLOF, R. The value of twin studies in epidemiology. World Medical Journal 14(6) : 168–171, November–December 1967.

S13. CHANG, K. M. Betel nut chewing and mouth cancer in Taiwan. Second Report : Observation of the oral mucosa in the betel nut chewer. Tai-wan I Hsueh Tsa Chih 65(2) : 79–86, Feb. 28, 1966.

S14. CHAPMAN, W. H. Effects of oral tobacco tar and a paraffin foreign body on the mouse bladder. Chapter 14. *In:* Bladder Cancer. Proceedings of the 5th Inter-American Conference on Toxicology and Occupational Medicine, University of Miami, School of Medicine, Coral Gables, Fla., 1966. Pp. 170–179.

S15. CLAYSON, D. B. Chemicals and environmental carcinogenesis in man. European Journal of Cancer 3(4/5) : 405–416, November 1967.

S16. CLAYSON, D. B. Human and experimental bladder cancer. Annali della Facolta de Medicina e Chirurgia della Universita degli Studi di Perugia che Pubblicano gli Atti della Accademia Anatomica-Chirurgica 57(4) : 502–520, July 31, 1967.

S17. Coal mining, pneumoconiosis, and lung cancer. British Medical Journal 4(5578) : 502–503, Dec. 2, 1967.

S18. COOPER, K. H., GEY, G. O., BOTTENBERG, R. A. Effects of cigarette smoking on endurance performance. Journal of the American Medical Association 203(3) : 189–192, Jan. 15, 1968.

S19. COORAY, G. H., LESLIE, N. D. G. Bronchial neoplasms among the Ceylonese. British Journal of Cancer 12(1) : 1–4, March 1958.

S20. DALHAMN, T., ROSENGREN, A. The effect of oxygen lack of the tracheal cillary activity. Archives of Environmental Health 16(3): 371–373, March 1968.

S21. DALHAMN, T., RYLANDER, R. Tar content and ciliotoxicity of cigarette smoke. Acta Pharmacologica et Toxicologica 25(3): 369–372, 1967.

S22. DAOUST, R. Les cancerologues a Tokio. (Editorial.) Union Medicale du Canada 96(1): 1–2, January 1967.

S23. DENK, W., HANSLUWKA, H., KARRER, K. Regionale Unterschiede in der Haufigkeit des Lungenkarzinoms in Osterreich. Weiner Medizinische Wochenschrift 118(4): 64–72, Jan. 27, 1968.

S24. DENOIX, P. Frequences des differents cancers. Le Concours Medical 89(2): 263–269, Jan. 14, 1967.

S25. DEVILLIERS, A. J. Cancer of the lung in a group of fluorspar miners. Canadian Cancer Conference 6: 460–474, 1966.

S26. DREXLER, J. Asymptomatic polyps of the rectum and colon. I. A reexamination. Archives of Internal Medicine 119(5): 503–509, May 1967.

S27. DREXLER, J. Asymptomatic polyps of the rectum and colon. II. Frequency, smoking, and arteriosclerotic heart disease. Archives of Internal Medicine 121(1): 62–66, January 1968.

S28. EGLIMEX, S., SAVAS, I. Brons kanserleri. Tip Fakultesi Mecmuasi 29: 487–492, 1966.

S29. EINHORN, J., WERSALL, J. Incidence of oral carcinoma in patients with leukoplakia of the oral mucosa. Cancer 20(12): 2189–2193, December 1967.

S30. EL-MOFTY, S. Oral cancer in the United Arab Republic. Oral Surgery, Oral Medicine and Oral Pathology 24(2): 240–245, August 1967.

S31. EPSTEIN, S. S. Carcinogenicity of organic extracts of atmospheric pollutants, Journal of the Air Pollution Control Association 17(11): 728–729, November 1967.

S32. FORGACS, J., CARLL, W. T. Mycotoxicoses: Toxic fungi in tobaccos. Science 152(3729): 1634–1635, June 17, 1966.

S33. FRESH, J. W., SUN, S. C., RAMPSCH, J. W. Nasopharyngeal carcinoma and environmental carcinogens. Unio Internationalis contra Cancrum Monograph Series 1(20): 124–129, 1967.

S34. GELBOIN, H. V., KLEIN, M., BATES, R. R. Inhibition of mouse skin tumorigenesis by Actinomycin D. Proceedings of the National Academy of Sciences of the United States of America 53(6): 1353–1360, June 1965.

S35. GEMANT, A. Cell invasiveness and carcinogenic hydrocarbons. Grace Hospital Bulletin 46(1): 3–9, January 1968.

S36. GOLDMAN, K. P. Mortality of coal-miners from carcinoma of the lung. British Journal of Industrial Medicine 22(1): 72–77, January 1965.

S37. GOLDMAN, K. P. Prognosis of coal-miners with cancer of the lung. Thorax 20: 170–174, 1965.

S38. GOLLEDGE, A. H., WICKEN, A. J. Local variation in the incidence of lung cancer and bronchitis mortality. Medical Officer 112: 273–277, Nov. 13, 1964.

S39. GRAHAM, S. Lung cancer as related to smoking behavior patterns. Presented at the American Public Health Association, Miami Beach, Fla., Oct. 26, 1967. [Unpublished.] 9 pp.

S40. GSELL, O. Epidemiologie des Bronchialkarzinoms. Erhebungen über die Umgebungseinflüsse in der Schweiz. Oncologia 19: 194–217, 1965.

S41. GSELL, O., STROEL, M. Maligne Tumoren in Beziehung zum Tabakrauchen. (9 Jahre Beobachtungen bei Arzten in der Schweiz.) Oncologia 20 (Supplement): 45–51, 1966.

S42. GUERNSEY, L. H. Squamous-cell carcinoma of the floor of the mouth arising from previously biopsied keratotic lesions. Oral Surgery, Oral Medicine and Oral Pathology 21(2) : 262–269, February 1966.

S43. HAMMOND, E. C. Epidemiological evidence on the effects of air pollution. Presented at the 60th Annual Meeting, Air Pollution Control Association, June 14, 1967, Cleveland, Ohio [Unpublished.] 27 pp.

S44. HAMMOND, E. C. Prospects in cancer epidemiology, and a theory on carcinogenesis. Environmental Research 1(1) : 102–113, June 1967.

S45. HARRISON, D. F. N. Snuff—Its use and abuse. British Medical Journal 2(5425) : 1649–1651, Dec. 26, 1964.

S46. HENSCHLER, D. Kanzerogene stoffe in pflanzen. Therpiewoche 17(43) : 1733–1738, Oct. 25, 1967.

S47. HORIE, A. KOHCHI, S., KURATSUNE, M. Carcinogenesis in the esophagus. II. Experimental production of esophageal cancer by administration of ethanolic solution of carcinogens. Gann 56(5) : 429–441, October 1965.

S48. HUDSON, P. B. Summary of development of the chemosol process as a fuel additive for cigarette tobacco and supporting chemical and biological test results. Subcommittee on Consumers, Senate Commerce Committee, Aug. 23, 1967. [Unpublished.] 11 pp.

S49. HUEPER, W. C. Occupational cancers of the lung in radioactive ore miners in U.S.A. *In:* Harris, R. J. C., editor. Proceedings of the Ninth International Cancer Congress. Unio Internationalis Contra Cancrum Monograph Series Volume 10. New York, Springer-Verlag, 1967. Pp. 143–146.

S50. KAMINSKI, E. J., FANCHER, O. E., CALANDRA, J. C. *In vivo* studies of the ciliastatic effects of tobacco smoke. Absorption of ciliastatic components by wet surfaces. Archives of Environmental Health 16(2) : 188–193, February 1968.

S51. KHANOLKAR, V. R. The story of the Indian Cancer Research Center, Parel, Bombay. Proceedings of the National Institute of Sciences of India, Part B : Biological Sciences 32(1/2) : 97–103, April 1966.

S52. KING, H., BAILAR, J. C. III. Epidemiology of urinary bladder cancer. A review of selected literature. Journal of Chronic Diseases 19(7) : 735–772, July 1966.

S53. KINOSHITA, S., SATO N., SAITO, N., NISHIDA, K., DAKE, F., HORIUCHI, Y. Intracutaneous tests with tobacco extracts and cardiovascular disease. Report I. With a special reference to coronary artery disease. Arerugi 16(11) : 729–733, November 1967.

S54. KNYCHALSKA-KARWAN, Z. Leukoplakia blony sluzoweg jamy ustnej. Folia Medica Cracoviensia 8(3) : 435–476, 1967.

S55. KOIVUNIEMI, A., HOLSTI, L. R. Cytologic population screening in the early detection of lung cancer. Annales Medicinae Internae Fenniae 56: 65–71, 1967.

S56. KROLLER, E. Ein Beitrag zur Beurteilung von Tabakzusatzstoffen auf Grund ihrer Pyrolyseprodukte. 3. Weissbrand- und Flottbrandmittel. Bundesgesunheitsblatt 9(22) : 333-334, 1966.

S57. KUNDU, P. N. Oral cancer and the dental surgeon. Journal of the Indian Medical Association 46(1) : 35–36, Jan. 1, 1966.

S58. LILIENFELD, A., ARCHER, P. G. BURNETT, C. H., CHAMBERLAIN, E. W., CHAZIN, B. J., DAVIES, D., DAVIS, R. L., HABER, P. A. HODGES, F. J., KOPROWSKA, I., KORDON, B., LANE, J. T., LAWTON, J. H., LEE, L., JR., MACCALLUM, D. B., MCDONALD, J. R., MILDER, J. W., NAYLOR, B., PAPANICOLAOU, G. N., SLUTZKER, B., SMITH, R. T. SWESTON, E. R., UMIKER, W. O. An evaluation of radiologic and cytologic screening for the early detection of lung cancer: A Cooperative pilot study of the American Cancer Society and

the Veterans Administration. Cancer Research 26(10) : 2083–2121, October 1966.

S59. LYNCH, G. A. Cancer of the lip. Ulster Medical Journal 36(1) : 44–50, 1967.

S60. MAS ISARRE, M., SOLSONA MOTREL, F. Atmosfera y Cancer. Medicina y Cirugia de Guerra 29(1) : 15–34, January 1967.

S61. MATTHEWS, D. M. Inter-relationships between smoking, cyanide metabolism, and vitamin B12 metabolism. London, Westminster Hospital, October 1967. [Unpublished.]

S62. MELCHIOR, E. Some aspects of the actual cancer problem. Proceedings of the Near and Middle East First International Cancer Congress, Ankara, Turkey, Sept. 10–15, 1965. Turkish Association for Cancer Research and Control, 1966. Pp. 9–15.

S63. MERRIMAN, J. E. Dynamic exercise tolerance tests: Effects in normal subjects of stopping smoking. (Abstract) Circulation 36(4) (Supplement II) : 186, October 1967.

S64. MOORE, C. Cancer of the mouth. Southern Medical Bulletin 54(2) : 15–22, June 1966.

S65. MOORE, C. Smoking and cancer of the mouth, pharynx, and larynx. Journal of the American Medical Association 191(4) : 283–286, Jan. 25, 1965.

S66. MORGAN, J. F., TOLNIA, S., TOWNSEND, G. F. Studies on the *in vitro* antitumor activity of fatty acids: II. Saturated dicarboxylic acids. Canadian Journal of Biochemistry and Physiology 38 : 597–603, 1960.

S67. MUNOZ, N., CORREA, P., BOCK, F. Comparative carcinogenic effect of two types of tobacco. Cancer 21(3) : 376–389, March 1968.

S68. Nonsmokers share carcinogenic risk while breathing air among smokers. Medical Tribune 8(117) : 2, Dec. 4, 1967.

S69. OETTEL, H. Erkrankungsrisiko des passiven Rauchens? Deutsche Medizinische Wochenschrift 92(44) : 2042–2043, Nov. 3, 1967.

S70. OGURA, J. H., MALLEN, R. W. Carcinoma of the larynx. Diagnosis and treatment. Postgraduate Medicine : 493–498, November 1963.

S71. Oropharyngeal Cancer in India. Lancet 1 : 1026, May 7, 1966.

S72. PAMUKOU, A. M. Etiology of bovine urinary bladder cancer. Proceedings of the Near and Middle East First International Cancer Congress, Ankara, Turkey, Sept. 10–15, 1965. Ankara, Turkish Association For Cancer Research and Control, 1966. Pp. 484–489.

S73. PEARSON, F. G., THOMPSON, D. W., DELARUE, N. C. Experience with the cytologic detection, localization, and treatment of radiographically undemonstrable bronchial carcinoma. Journal of Thoracic and Cardiovascular Surgery 54(3) : 371–382, September 1967.

S74. PETERSON, G. F. Cancer of the lung in Iceland. A study on cases diagnosed during the period 1931–1957. Acta Radiologica (Supplement 188) : 198–209, 1959.

S75. PINDBORG, J. J., KIAER, J., GUPTA, P. C., CHAWLA, T. N. Studies in oral leukoplakias. Prevalence of leukoplakia among 10,000 persons in Lucknow, India, with special reference to use of tobacco and betel nut. Bulletin of the World Health Organization 37 : 109–116, 1967.

S76. PINDBORG, J. J. POULSEN, H. E. Studies in oral leukoplakias. 1. The influence of snuff upon the connective tissue of the oral mucosa. Preliminary report. Acta Pathologica et Microbiologica Scandinavica 55: 412–414, 1962.

S77. PINDBORG, J. J. POULSEN, H. E. ZACHARIAH, J. Oral epithelial changes in thirty Indians with oral cancer and submucous fibrosis. Cancer 20: 1141–1146, July 1967.

S78. PINDBORG, J. J., RENSTRUP, G. Studies in oral leukoplakias. II. Effect of snuff on oral epithelium. Acta Dermato-Venerelogica 43: 271–276, 1963.

S79. PLAZA, F., AVELLO, A. Carcinoma del labio. Acta Cancerologica 5(2): 49–56, 1966.

S80. POKRANT, H., WORNIALLO, M. Badania cytologiczne blony sluzowej jamy ustnej u nalogowych palaczy tytoniu. Czasopismo Stomatolginze 20(2): 139–143, 1967.

S81. QUIGLEY, L. F., Jr., SHKLAR, G., COBB, C. M. Reverse cigarette smoking in Caribbeans: Clinical, histologic, and cytologic observations. Journal of the American Dental Association 72: 867–873, April 1966.

S82. RAMIREZ, D. F., NADAL, H. M., ESCANAVERINO, R. B. Carcinoma of the oral cavity and pharynx. Boletin de la Asociacion Medica de Puerto Rico 59(4): 188–195, April 1967.

S83. ROBERTS, J. A. F. Snuff (letter). British Medical Journal 1: 187–188, Jan. 16, 1965.

S84. RUDDON, R. W. Alteration of enzyme induction patterns in rats with the carcinogen dimethylnitrosamine. Life Sciences 6(21): 2299–2306, Nov. 1, 1967.

S85. SAFFIOTTI, U. Lung Cancer: An experimental approach. Cancer Bulletin 19(4): 72–73, July–August 1967.

S86. SAFFIOTTI, U., CEFIS, F., KOLB, L. H. A method for the experimental induction of bronchogenic carcinoma. Cancer Research 28(1): 104–124, January 1968.

S87. SAFFIOTTI, U., CEFIS, F., SHUBIK, P. Histopathology and histogenesis of lung cancer induced in hamsters by carcinogens carried by dust particles. *In:* Severi, L., editor. Lung Tumours in Animals. Perugia, Italy, Division of Cancer Research, University of Perugia, June 1966. Pp. 537–546.

S88. SCHIEVELBEIN, H., GRUMBACH, H. Der Einfluss von Tabakrauchbestandteilen auf den Tryptophanstoffwechsel. Zeitschrift fur Krebsforschung 70(1): 48–54, 1967.

S89. SCHIEVELBEIN, H., GRUMBACH, H. The influence of tobacco smoke components on the activity of kynureninase, Chapter 15. *In:* Bladder Cancer. Proceedings of the 5th Inter-American Conference on Toxicology and Occupational Medicine, University of Miami, School of Medicine, Coral Gables, Fla., 1966. Pp. 180–186.

S90. SCHMITT, C. K., FOLSOM, T. C. Histologic evaluation of degenerative changes of the lower lip. Journal of Oral Surgery 26(1): 51–56, January 1968.

S91. SELTZER, C. C. An evaluation of the effect of smoking on coronary heart disease. I. Epidemiological evidence. Journal of the American Medical Association 203(3): 193–200, Jan. 15, 1968.

S92. SHEDD, D. P., VON ESSEN, C. F., CONNELLY, R. R., EISENBERG, H. Cancer of the buccal mucosa, palate and gingiva in Connecticut, 1935–1959. Cancer 21(3): 440–446, March 1968.

S93. SHEDD, D. P., VON ESSEN, C. F., CONNELLY, R. R., EISENBERG, H. Cancer of the floor of the mouth in Connecticut, 1935–1959. Cancer 21(1): 97–101, January 1968.

S94. SHEDD, D. P., VON ESSEN, C. F., CONNELLY, R. R., EISENBERG, H. Cancer of the pharynx in Connecticut, 1935–1959. Cancer 21(4): 706–713, April 1968.

S95. SHEDD, D. P., VON ESSEN, C. F., FERRARO, R. H., CONNELLY, R. R. EISENBERG, H. Cancer of tongue in Connecticut, 1935–1959. Cancer 21(1): 89–96, January 1968.

S96. SIRSAT, M. V., DOCTOR, V. M. A histopathologic study on the effect of tobacco chewing on the buccal mucosa in Indians and its relationships to cancer. British Journal of Cancer 21: 277–284, 1967.

S97. Smoke and naspharyngeal cancer. Lancet 2(7417): 833–834, Oct. 23, 1965.

S98. STEWART, W. H. Smoking and health: A progress report. Presented at the 8th Annual American Cancer Society Science Writers' Seminar, Phoenix, Arizona, Mar. 29, 1966. [Unpublished.] 10 pp.

S99. STEWART, W. H. Statement before the Consumer Subcommittee of the Committee on Commerce. U.S. Senate, Aug. 25, 1967. 10 pp.

S100. TAGLIAFERRO, E., FRANCA, F. Fumo di tabacco e cancro bronco-pulmonare. Minerva Medica Guiliana 7(1): 78–80, January–March 1967.

S101. TAUBENHAUS, L. J., MALOOF, E. C., SCANLON, J. W. Smoking and oral pathology: An epidemiologic study. Journal of the American Geratrics Society 12(9): 871–876, September 1964.

S102. TOLNAI, S., MORGAN, J. F. Studies on the *in vitro* antitumor activity of fatty acids: III. Saturated monocarboxylic acids. Canadian Journal of Biochemistry and Physiology 39: 713–719, 1961.

S103. TOWNSEND, G. F., MORGAN, J. F., TOLNAI, S. HAZLETT, B., MORTON, H. J., SHUEL, R. W. Studies on the *in vitro* antitumor activity of fatty acids. I. 10-Hydroxy-2-decanoic acid from royal jelly. Cancer Research 20: 503–510, May 1960.

S104. U.S. PUBLIC HEALTH SERVICE. Cancer of the mouth. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1461, 1966. 6 pp.

S105. URAGODA, C. G. Incidence of bronchial carcinoma in a Ceylon chest clinic. British Journal of Diseases of the Chest 61: 154–158, July 1967.

S106. VILENKINA, G. YA., CHERKES, L. D. Soderzhanie nukleinovykh kislot v pecheni krys, poluchavshikh s pishchey selen. Voprosy Piteniia 25(1): 30–33, 1966.

S107. VOGLER, W. R., LLOYD, J. W., MILMORE, B. K. A retrospective study of etiological factors in cancer of the mouth, pharynx, and larynx. Cancer 15(2): 246–258, March–April 1962.

S108. WACHSMUTH, W., VIERECK, H. J. Fumo e carcinoma bronchiale. Terapia 50: 185–188, September–October 1965.

S109. WAHI, P. N., KAPUR, V. L., LUTHRA, U. K., SRIVASTAVA, M. C. Submucous fibrosis of the oral cavity: 2. Studies on epidemiology. Bulletin of the World Health Organization 35(5): 793–799, November 1966.

S110. WEY, W., PFALTZ, C. R. Schadigungen der schleimhaut der oberen Luft- und speisewege durch Tabak. Praxis 55: 182–184, February 1966.

S111. WYNDER, E. L., SHIGEMATSU, T. Environmental factors of cancer of the colon and rectum. Cancer 20(9): 1520–1561, September 1967.

S112. YASHAR, J. J., GURALNICK, E., MCAULEY, R. L. Multiple malignant tumors of the oral cavity, respiratory system, and upper digestive system. Experience at the Pondville State Hospital from 1949 to 1959. American Journal of Surgery 112(1): 70–75, July 1966.

S113. ZANOLLI, M., PUELMA, H. O., ONETO, J. Primary bronchogenic carcinoma. Diseases of the Chest 53(2): 183–185, February 1968.

S114. ZECHNER, G. Zum Problem des Raucherkehlkopps. Acta Oto-Laryngologica (Supplement 224): 521–530, 1967.

S115. ZIMMERMANN, E. R., ZIMMERMANN, A. L. Effects of race, age, smoking habits, oral and systemic disease on oral exfoliative cytology. Journal of Dental Research 44(4): 627–631, July–August 1965.

U.S. GOVERNMENT PRINTING OFFICE: 1968 O—315–131