The Health Consequences of SMOKING

1969 SUPPLEMENT TO THE

1967 Public Health Service Review

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Foreword

This is the third report required by Section 5(d)(1) of the Federal Cigarette Labeling and Advertising Act, which directs the Secretary of Health, Education, and Welfare to submit annual reports to the Congress on the health consequences of smoking. The preceding two reports were *The Health Consequences of Smoking, A Public Health Service Review: 1967* and *The Health Consequences of Smoking, 1968 Supplement to the 1967 Public Health Service Review.*

The present Supplement was submitted to the Congress on July 29, 1969.

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PART 1

Current Information on the Health Consequences of Smoking

Summary of the Report

This report is a review of the pertinent medical literature on the health consequences of smoking which has appeared since the publication of the 1968 Supplement to the 1967 Public Health Service Review. The 1964 Report of the Advisory Committee on Smoking and Health, the 1967 Public Health Service Review, and the 1968 Supplement have presented the broad base of converging epidemiological, physiological, pathological, and clinical evidence on which knowledge of the health hazards of smoking is based. Included in this evidence are data which show the magnitude of the excess mortality and morbidity among smokers.

The following conclusions regarding the health consequences of smoking were summarized in the 1968 Supplement:

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.

The most recent Public Health Service review of the effects of smoking on pregnancy was presented in the 1967 Report. The conclusions of that review were as follows:

Clearly, more research is needed to elucidate the significance of the relationship of smoking in pregnancy and low birth weight. Additional long-range morbidity studies are needed, as well as studies on the effect of smoking on uterine activities and placental blood flow.

Smoking does have an effect on the outcome of pregnancy. However, it is not known whether this effect is deleterious or not.

Until such evidence is presented so as to clearly define the role of smoking in pregnancy, it is more prudent at this time to advise pregnant women to stop or decrease their cigarette-smoking practices.

No substantial negative evidence has appeared which refutes these judgments. On the contrary, studies made available since the publication of the 1968 Supplement and reviewed by panels of experts in the relevant medical areas confirm previous findings and add new evidence that smoking is a health hazard. Highlights of the 1969 Supplement are as follows:

I. Smoking and Cardiovascular Diseases

Further data from prospective studies confirm the judgment that cigarette smoking is a significant risk factor that contributes to the development of coronary heart disease, apparently by promoting myocardial infarct and cardiac arrhythmias. Analyses by several investigators of other associated factors (high serum cholesterol, high blood pressure and body weight) show clearly that the effect of cigarette smoking persists and is appreciable, even when these other factors are carefully evaluated. Autopsy studies suggest that cigarette smoking is associated with a significant increase in atherosclerosis of the aorta and the coronary arteries. Experimental studies in animals have pro-

vided new information on the pathological effects of cigarette smoking on the arteries. This further supports the view that cigarette smoking promotes atherosclerosis.

II. Smoking and Chronic Obstructive Bronchopulmonary Diseases

Recent studies have demonstrated that cigarette smokers may have significant disease of the small airways in the absence of bronchopulmonary symptoms. This disease is demonstrated by the finding of abnormalities in the ventilation/perfusion relationships in the lungs of cigarette smokers. Animal experiments have demonstrated the pathological effects caused in the lung by exposure to cigarette smoke or to specified concentrations of products found in cigarette smoke. Conditions similar to pulmonary emphysema in man have been produced in some of these experiments. Other studies have investigated the pathological effects of smoking on pulmonary clearance mechanisms and demonstrated that pulmonary clearance may be significantly impaired by the effects of cigarette smoking. Epidemiological and laboratory evidence supports the view that cigarette smoking can contribute to the development of pulmonary emphysema in man.

III. Smoking and Cancer

A major pathological study of histological changes in the larynx has demonstrated a dose-relationship between smoking and premalignant changes in the larnyx. New animal models for the experimental study of respiratory cancer, which may be helpful in elucidating the mechanisms of respiratory tract carcinogenesis, have been developed and refined. More studies have been done to identify those substances in tobacco smoke which take part in carcinogenesis. These studies may help to define the exact biomechanisms involved in the cause and effect relationship between cigarette smoking and lung cancer.

IV. Effect of Smoking on Pregnancy

New data are presented which confirm the finding that maternal smoking during pregnancy is associated with low birth weight in infants and also indicate that maternal smoking is associated with an increased incidence of prematurity defined by weight alone. In addition, it appears that maternal smoking during pregnancy may be associated with an increased incidence of spontaneous abortion, stillbirth, and neonatal death and that this relationship may be most marked in the presence of other risk factors.

V. Smoking and Noncancerous Oral Disease

The chapter on noncancerous oral disease is the first Public Health Service review of this subject. The data available lead to the conclusion that ulceromembranous gingivitis, alveolar bone loss, and stomatitis

nicotina are more commonly found among smokers than among nonsmokers. The influence of smoking on periodontal disease and gingivitis probably operates in conjunction with poor oral hygiene. In addition, there is evidence that smoking may be associated with edentulism and delayed socket healing.

Tobacco smoke contains a large number and a wide variety of compounds which may result in complex and multiple pathophysiological effects on the various tissues and organ systems. While further research is needed to investigate the exact biomechanisms involved in the pathological effects of smoking, the evidence clearly shows that cigarette smoking constitutes a major health hazard in the United States.

PART 2

Technical Reports on the Relationship of Smoking to Specific Disease Categories

360-928 O—69——2

CHAPTER 1

Smoking and Cardiovascular Diseases

Contents

Summary

Coronary heart disease (CHD) among men in the Western world is an epidemic which cuts short the lives of many in their prime productive years. The evidence linking smoking and CHD has been reported not only from studies in the United States, but also from such diverse areas as West Germany, the U.S.S.R., France, Israel, Italy, and the British Isles.

The 1968 Supplement (*27*) stated:

> 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.

The convergence of autopsy data and experimental data presented in this and previous reports suggests that cigarette smoking promotes atherosclerosis, including that of the coronary arteries. The results of physiological research and the findings of diminished risk of CHD in those who have stopped smoking indicate that there is also a more immediate mechanism operative. The mechanisms which might be responsible for the promotion of myocardial infarction and fatal cardiac arrhythmias by cigarette smoking were extensively reviewed in the 1968 Supplement (*27*). Briefly stated, nutrient supply to the myocardium in general and, perhaps more importantly, to focal ischemic areas of the myocardium may be seriously compromised by a combination of effects caused by smoking, and the deprived myocardium may become infarcted or develop an arrhythmia. These effects include diminution of blood flow through atherosclerotic coronary vessels and diminution of available oxygen for tissue use resulting from the binding of carbon monoxide to hemoglobin in the place of oxygen and

possibly, although presently speculative, the poisoning of respiratory enzymes by hydrogen cyanide.

Cigarette smoking has been shown to be an important risk factor in the development of CHD. It is important both by itself and in the presence of other significant risk factors. In combination with certain other risk factors, the joint effects appear to be even greater than those accounted for by those risk factors independently.

Epidemiological Studies

Hammond, et al. (*11*) have presented new data on mortality from CHD, stroke, and nonsyphilitic aortic aneurysm among more than 800,000 men and women who were between the ages of 40 and 79 in 1959. The authors were attempting to evaluate the significance of multiple factors (sex, age, diabetes, high blood pressure, body weight, change in weight, exercise, cigarette smoking, sleep, and nervous tension) in the variations in death rates from these three diseases. It should be noted that this information consisted of self-reports obtained by questionnaire and were not obtained from medical examination. Causes of death were based on death certificate reports.

As illustrated in table 1, coronary heart disease death rates and mortality ratios increased with increased cigarette smoking for men in all age groups and for women under the age of 70. Although the mortality ratios were higher in the younger age groups, the differences in death rates between nonsmokers and heavy smokers became progressively higher with increasing age. Although CHD rates were higher for those who were 10 percent or more above the average weight for their height-age-sex group, and for those who reported having high blood pressure, the trend is clear that the effect of smoking persists and is appreciable, even when these other factors are held constant (table 2).

TABLE 1.—*Death rates and mortality ratios for coronary heart disease and stroke, by amount of cigarette smoking, sex, and age*

Sex and age	Coronary heart disease					Stroke				
	Never smoked cigarettes regularly	Regularly smoked cigarettes				Never smoked cigarettes regularly	Regularly smoked cigarettes			
		Number smoked daily					Number smoked daily			
		1–9	10–19	20–39	40 or more		1–9	10–19	20–39	40 or more
	DEATH RATES									
Males:										
40–49 years	68	109	176	256	375	14	39	[2] 16	31	23
50–59 years	257	409	548	616	718	40	78	59	81	96
60–69 years	650	961	1,184	1,241	1,166	168	219	242	272	289
70–79 years	1,730	1,970	2,431	2,573	2,548	650	617	598	792	[2] 445
Females:										
40–49 years	13	17	27	47	[2] 43	10	15	26	29	[2] 57
50–59 years	59	68	140	158	220	27	34	73	72	[2] 95
60–69 years	268	279	479	558	[2] 542	110	139	236	201	--
70–79 years	979	740	963	1,243	---	487	404	[2] 276	622	--
	MORTALITY RATIOS [1]									
Males:										
40–49 years	1.00	1.60	2.59	3.76	5.51	1.00	2.79	[2] 1.14	2.21	1.64
50–59 years	1.00	1.59	2.13	2.40	2.79	1.00	1.95	1.48	2.03	2.40
60–69 years	1.00	1.48	1.82	1.91	1.79	1.00	1.30	1.44	1.62	1.72
70–79 years	1.00	1.14	1.41	1.49	1.47	1.00	.95	.92	1.22	[2] .68
Females:										
40–49 years	1.00	1.31	2.08	3.62	[2] 3.31	1.00	1.50	2.60	2.90	[2] 5.70
50–59 years	1.00	1.15	2.37	2.68	3.73	1.00	1.26	2.70	2.67	[2] 3.52
60–69 years	1.00	1.04	1.79	2.08	[2] 2.02	1.00	1.26	2.15	1.83	----
70–79 years	1.00	.76	.98	1.27	----	1.00	.83	[2] .57	1.28	----

[1] The mortality ratio is the observed rate divided by the expected rate.

[2] Rates based upon only 5 to 9 deaths.

SOURCE: Hammond, E. C., et al. (*11*).

TABLE 2.—*Coronary heart disease death rates for men and women classified by smoking habits, age, blood pressure, and relative weight*

Extent of cigarette smoking and age	No high blood pressure, by relative weight					High blood pressure, by relative weight				
	Total	Less than 90	90–109	110–119	120 and over	Total	Less than 90	90–109	110–119	120 and over
	MEN									
None or slight:										
40–49 years	52	[1] 27	46	64	128	204	---	195	[1] 210	-----
50–59 years	226	140	216	263	390	620	[1] 686	611	643	609
60–69 years	603	542	573	701	763	1,503	1,777	1,295	1,860	1,855
70–79 years	1,611	1,467	1,555	1,840	1,868	2,738	3,342	2,588	2,651	3,100
Intermediate:										
40–49 years	116	108	104	141	245	249	[1] 354	266	[1] 286	-----
50–59 years	373	352	363	405	538	876	1,424	686	1,182	995
60–69 years	888	814	890	984	973	1,876	1,913	1,999	1,447	1,710
70–79 years	1,973	2,237	1,778	1,953	2,901	3,220	3,700	3,172	2,213	5,451
20 or more:										0
40–49 years	222	123	235	309	276	647	687	550	765	888
50–59 years	530	422	536	666	641	1,137	1,148	1,153	933	1,41
60–69 years	1,047	978	1,019	1,249	1,307	1,986	2,160	1,993	1,744	2,075
70–79 years	2,286	2,346	2,205	2,151	2,846	4,123	5,141	4,205	[1] 3,692	-----
	WOMEN									
None or slight:										
40–49 years	8	[1] 5	7	---	22	63	---	53	-----	75
50–59 years	41	39	32	64	68	161	100	142	157	229
60–69 years	201	153	191	265	323	469	400	495	462	469
70–79 years	776	832	779	667	754	1.338	1,313	1,217	1,449	1,626
Intermediate:										
40–49 years	15	17	12	---	---	86	---	[1] 76	-----	-----
50–59 years	76	69	70	153	[1] 73	281	361	281	[1] 233	[1] 198
60–69 years	284	337	244	422	---	730	732	743	848	[1] 484
70–79 years	607	736	551	---	---	1,161	[1] 1,854	1,014	-----	-----
20 or more:										
40–49 years	36	25	38	[1] 42	[1] 73	144	---	198	-----	-----
50–59 years	120	118	128	---	[1] 135	358	[1] 263	291	[1] 584	[1] 706
60–69 years	467	341	539	[1] 637	---	811	[1] 798	1,100	-----	-----
70–79 years	644	[1] 866	[1] 585	---	---	2,463	---	[1] 3,743	-----	-----

[1] Rates based upon only 5 to 9 deaths.

SOURCE: Hammond, E. C., et al. (*11*).

Hammond, et al. also studied CHD mortality among men who were ex-smokers of cigarettes. The death rates from CHD were lower among the ex-smokers than among those still smoking at the beginning of the study, the size of the difference being larger the longer they had been off smoking (table 3). Some people stop smoking because of illness or symptoms and these people would be expected to have higher death rates than those who stop for other reasons. Early deaths among those with preexisting disease may account, at least in part, for the high death rates from CHD among ex-smokers in the early years of abstention.

Mortality ratios for stroke were higher among cigarette smokers with the exception of those over 70 years of age. Male ex-cigarette smokers had mortality ratios for stroke approximately equal to those of nonsmokers.

A clear increase in mortality from nonsyphilitic aortic aneurysms with increasing cigarette smoking among men aged 50–69 is seen in table 4. The mortality ratio for heavy smokers was 8.00.

Hammond, et al. found that death rates from the three diseases varied considerably with relative weight, amount of exercise, amount of cigarette smoking, and hours of sleep per night. Subjects who were obese, took little or no exercise, smoked many cigarettes a day, or slept 9 or more hours per night had high death rates. Those with a combination of these factors have especially high death rates from the three diseases.

TABLE 3.—*Observed and expected number of deaths and mortality ratios for ex-cigarette smokers with a history of smoking only cigarettes, by number of years since last cigarette smoking and for current cigarette smokers, coronary heart disease and stroke; compared to persons who never smoked regularly, in men aged 40–79*

Type of smoker	Coronary heart disease			Stroke		
	Observed	Expected	Ratio	Observed	Expected	Ratio
Ex-cigarette smokers (former smokers of 1–19 cigarettes a day):						
Stopped:						
Less than 1 year	29	17.9	1.62	------	------	------
1–4 years	57	46.6	1.22	------	------	------
5–9 years	55	43.7	1.26	------	------	------
10–19 years	52	54.1	.96	------	------	------
20 or more years	70	64.7	1.08	------	------	------
Total	263	226.9	1.16	57	56.9	1.00
Current cigarette smokers	1,063	559.5	1.90	207	134.5	1.54
Never smoked regularly	1,841	1,841.0	1.00	501	501.0	1.00
Ex-cigarette smokers (former smokers of 20 or more cigarettes a day):						
Stopped:						
Less than 1 year	62	38.6	1.61	------	------	------
1–4 years	154	101.9	1.51	------	------	------
5–9 years	135	116.5	1.16	------	------	------
10–19 years	133	106.1	1.25	------	------	------
20 or more years	80	76.4	1.05	------	------	------
Total	564	439.7	1.28	94	101.1	0.93
Current cigarette smokers	2,822	1,104.7	2.55	440	234.7	1.87
Never smoked regularly	1,841	1,841.0	1.00	501	501.0	1.00

SOURCE: Hammond, E. C., et al. (*11*).

TABLE 4.—*Aortic aneurysm death rates and mortality ratios for men aged 50–69, classified by cigarette smoking habits*

[Rates per 1,000 population]

Measure	Never smoked regularly	Current smokers, by daily cigarette consumption			
		1–9	10–19	20–39	40 or more
Death rate	13	34	50	59	104
Mortality ratio	1. 00	2. 62	3. 85	4. 54	8. 00

SOURCE: Hammond, E. C., et al. (*11*).

They also found that death rates from CHD and stroke were lower in ex-cigarette smokers than in men who were currently smoking cigarettes at the time they enrolled in the study. The death rates of male ex-cigarette smokers who had not smoked for 10 to 20 years were no higher or only slightly higher than the death rates of men who had never smoked regularly. Death rates from the three diseases were lowest among subjects without a history of diabetes or high blood pressure who were not obese, took at least moderate exercise, never smoked regularly and slept 6 to 8 hours per night. Nevertheless, even these subjects had substantial death rates from CHD, stroke and nonsyphilitic aortic aneurysm.

Stamler (*24*) has anaylzed 10-year mortality data on a total cohort of men, aged 40–59 in 1958, who were employees of the Chicago Peoples Gas Light and Coke Co. Of 1,465 men examined, 1,325 were found initially to be free of definite CHD and have been followed without systematic intervention. Higher overall death rates were found among the smokers in the study. Table 5 shows the death rates from CHD and from all causes for men with various risk factors.

Recent papers by Thorne, et al. (*25*) and by Paffenbarger, et al. (*19*) report further results of studies of CHD among former college students. College health records and other college records were reviewed to ascertain the presence or absence of factors under consideration. Cases were identified from death certificates in the study of fatal CHD (*19*) and from questionnaires and physical examinations in the study of nonfatal CHD (*25*). Matched controls were obtained for each case. In both nonfatal and fatal CHD, significantly more smokers were found among the cases than among the controls. Combinations of risk factors resulted in greater CHD morbidity and mortality ratios than did single factors. Figure 1 shows the morbidity ratios for combinations of pairs of risk factors in nonfatal CHD and table 6 shows mortality ratios for combinations of risk factors in fatal CHD.

TABLE 5.—*10-year mortality rates for sudden death, coronary heart disease, stroke, cardiovascular-renal, and all causes combined among men aged 40–59, classified according to cigarette smoking, cholesterol, and blood pressure*

[Peoples Gas Light Co. Study, 1958–68. Men originally free of coronary heart disease and followed without systematic intervention.]

1958 risk factor status—cigarette smoking (10 or more a day), hypercholesterolemia, hypertension [1]	10-year mortality										
	Sudden death			All CHD		Stroke		All CVR		All causes	
	Number of mean in cohort	Number of deaths	Death rate [2]	Number of deaths	Death rate	Number of deaths	Death rate	Number of deaths	Death rate	Number of deaths	Death rate
No risk factor	284	0	0	1	3.0	2	5.9	4	11.9	13	42.6
Hypercholesterolemia or hypertension only—1 factor	216	4	19.6	13	53.1	6	19.5	19	72.6	27	101.5
Cigarette smoking only (10 or more a day)—1 factor	405	4	10.0	15	37.1	5	11.8	20	48.9	44	107.7
Hypercholesterolemia and hypertension only—2 factors	60	1	9.9	3	29.6	1	40.7	4	70.3	8	121.9
Cigarette smoking (10 or more a day) and hypercholesterolemia or cigarette smoking and hypertension—2 factors	293	11	37.2	17	57.1	6	19.9	26	86.4	53	169.9
Cigarette smoking (10 or more a day), hypercholesterolemia, hypertension—all 3	67	2	25.1	6	76.0	2	25.4	8	101.5	17	225.8
Total	[3] 1,325	22	16.2	55	39.2	22	14.9	81	56.6	162	113.1

[1] Risk factors include: Serum cholesterol 250 or more mg./dl.; diastolic blood pressure 90 or more mm. Hg; 10 or more cigarettes/day.

[2] All rates are age-adjusted by 5-year age groups to the U.S. male population, 1960. All rates per thousand.

[3] Smoking data were not obtained for 4 of the 1,329 men.

SOURCE: Stamler, J. (*84*).

TABLE 6.—*Estimated coronary heart disease death ratios in a 17–51 year followup among former college students, classified according to combined presence (+) or absence (—) of each of three specified risk factors, and by age*

Risk factor			Age (years) at death from coronary heart disease			
Cigarettes, 10 or more/day	Systolic BP, 130 or more mm. Hg	Ponderal index, less than 12.9	Total 30–69 years	30–44 years	45–54 years	55–69 years
+	+	+	4.3	[1] (1.9)	5.7	[1] (4.8)
+	—	+	1.8	2.3	1.6	[1] (2.0)
+	+	—	4.2	2.9	4.5	5.6
—	+	+	1.9	2.9	1.6	1.8
+	—	—	1.7	2.2	1.9	1.3
—	+	—	1.3	1.2	1.2	1.4
—	—	+	1.1	1.4	1.4	.8
—	—	—	1.0	1.0	1.0	1.0

[1] Numbers in parentheses indicate expected number coronary heart disease decedents less than 5.

SOURCE: Paffenbarger, R. S., et al. (*19*).

In a study of participants in the Health Insurance Plan of New York, Weinblatt, et al. (*29*) reported that cigarette smoking males who developed angina pectoris were more likely to develop infarction than were nonsmoking anginal patients, but there were not enough cases to draw definite conclusions.

Weinblatt, et al. (*30*) also reported that the prognosis after the development of a myocardial infarction appears to be independent of smoking status prior to the infarct. In the absence of data indicating which patients stop smoking and how stopping smoking is related to the severity of myocardial damage, one cannot evaluate the effect of smoking on prognosis. If the persons who stop smoking tend to include the most debilitated, the effect of continued smoking on prognosis would be underestimated.

In a prospective study of over 3,000 men, Jenkins, et al. (*14*) reported that the incidence of CHD in men aged 39–49 was three times higher among the cigarette smokers than among the nonsmokers (table 7). The incidence of CHD increased with increased daily cigarette consumption. For men aged 50–59, the relationship between cigarette smoking and CHD was found to be significant only for the heavy

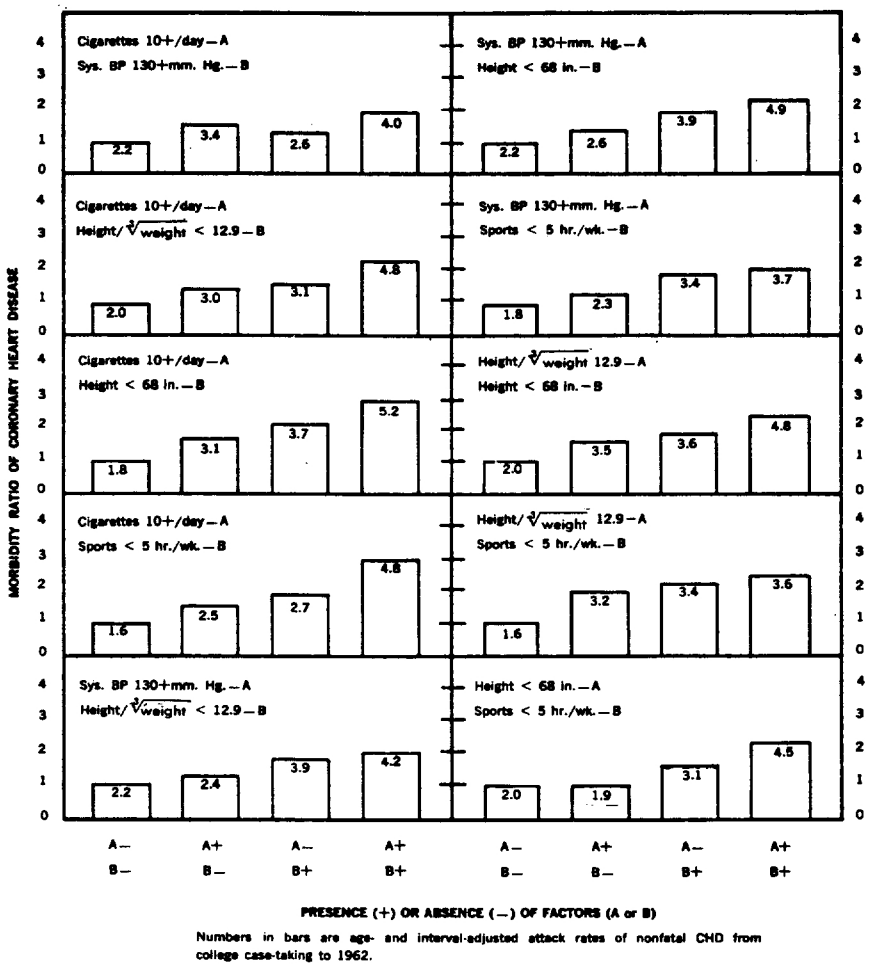

FIGURE 1.—Morbidity ratios of coronary heart disease for paired combinations of factors in college.

SOURCE: Thorne, M.C., et al. (*25*).

smokers (table 8). Former cigarette smokers also had significantly higher CHD incidence rates, but no data are given on length of time since stopping smoking, or reasons for stopping. Pipe and cigar smokers did not have higher CHD incidence rates. After controlling for other risk factors such as lipid levels, diastolic blood pressure, and body build, the authors found that the association between cigarette smoking and CHD remained (tables 9, 10). The relationship between smoking and CHD was stronger among those men who exhibited behavior type A than those exhibiting behavior type B (tables 11, 12). Behavior type A is characterized by enhanced competitiveness, drive, aggressiveness, hostility, and an excessive sense of time urgency. Behavior type B indicates an absence of these characteristics. Analysis of the data on behavior and cigarette smoking showed that both factors have effects on the CHD rate. Again, these associations were stronger in the younger age group.

TABLE 7.—*Annual incidence rates of coronary heart disease for men 39–49 years of age, classified by smoking history and by current practices as to cigarette smoking*

[Age as of the beginning of the 4½ year period of observation]

Morbidity status	Total subjects		Smoking history								Current cigarette smoking by number per day							
			Never smoked		Pipe and cigar only		Former cigarette		Current cigarette		None		1–15		16–25		26 or more	
	Number	Rate [1]	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Total number at risk	2,258	-----	540	-----	405	-----	239	-----	1,074	-----	1,191	-----	211	-----	434	-----	422	-----
Total number CHD cases	63	6.2	7	[2] 2.9	3	1.6	10	[2] 9.3	43	[2] 8.9	20	[2] 3.7	5	5.3	18	[4] 9.2	20	[4] 10.5
All myocardial infarction	52	5.1	4	1.7	3	1.6	10	9.3	35	7.2	17	3.1	4	4.2	13	6.7	18	9.5
Symptomatic	38	3.7	1	.4	2	1.1	8	7.4	27	5.6	11	2.0	4	4.2	11	5.6	12	6.3
Unrecognized	14	1.4	3	1.2	1	.5	2	1.9	8	1.7	6	1.1	0	0	2	1.0	6	3.1
Fatal	9	.9	0	0	0	0	1	.9	8	1.7	1	.2	0	0	5	2.6	3	1.6
Angina pectoris only	11	1.1	3	1.2	0	0	0	0	8	1.7	3	.6	1	1.0	5	2.6	2	1.1

[1] Annual rate per 1,000 men at risk.

[2] These distributions of cases for various smoking categories are significantly different from chance at P=0.001.

[3] Difference in CHD frequency between this group and those who never smoked cigarettes (col. 1 and 2 combined) is significant at P=0.01 by chi square test corrected for continuity.

[4] Difference in CHD frequency between this group and current noncigarette smokers is significant at P=0.01.

SOURCE: Jenkin, C. D., et al. (*14*).

TABLE 8.—*Annual incidence rates of coronary heart disease for men 50–59 years of age, classified by smoking history and by current practices as to cigarette smoking*

[Age as of the beginning of the 4½ year period of observation]

Morbidity status	Total subjects		Smoking history								Current cigarette smoking by number per day							
			Never smoked		Pipe and cigar only		Former cigarette		Current cigarette		None		1–15		16–25		26 or more	
	Number	Rate [1]	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Total number at risk	924	-----	182	-----	161	-----	137	-----	444	-----	483	-----	109	-----	167	-----	165	-----
Total number CHD cases	70	16.8	9	[2] 11.0	11	15.2	9	14.6	41	20.5	29	[2] 13.3	6	12.2	16	21.3	[3] 19	25.6
All myocardial infarction	52	12.5	6	7.3	8	11.0	5	8.1	33	16.5	19	8.7	5	10.2	15	20.0	13	17.5
Symptomatic	35	8.4	4	4.9	4	5.5	4	6.5	23	11.5	12	5.5	4	8.2	11	14.6	8	10.8
Unrecognized	17	4.1	2	2.4	4	5.5	1	1.6	10	5.0	7	3.2	1	2.0	4	5.3	5	6.7
Fatal	14	3.4	0	0	3	4.1	3	4.9	8	4.0	6	2.8	2	4.1	4	5.3	2	2.7
Angina pectoris only	18	4.3	3	3.7	3	4.1	4	6.5	8	4.0	10	4.6	1	2.0	1	1.3	6	8.1

[1] Annual rate per 1,000 men at risk.

[2] These distributions of cases for various smoking categories could occur 0.10 of the time by chance, hence are not significant at P=0.05.

[3] Difference in CHD frequency between this group and current noncigarette smokers is significant at P=0.01.

SOURCE: Jenkins, C. D., et al. (*14*).

TABLE 9.—*Annual incidence rates of new coronary heart disease, by smoking habits, adjusted for age and seriatim, for specified other risk factors*

[Rates are annual incidence per 1,000 men, aged 39 to 49 years at entry into study]

Specified other risk factors	Never smoked	Former cigarette smokers	Pipe and cigar only	Daily cigarette consumption			p.[1]
				1–15	16–25	26 or more	
Cholesterol	33	93	22	49	89	100	0.005
Beta/alpha ratio	31	91	18	49	91	102	.001
Lipalbumin	31	95	18	51	89	102	.002
Systolic BP	31	91	18	49	95	100	.001
Diastolic BP	29	89	16	49	95	104	.001
Ponderal index	29	91	16	49	95	107	.001
Physical activity	29	93	18	47	93	104	.001
Amount of exercise	29	91	18	49	93	104	.001
Income level	29	91	18	49	93	104	.001
All of the above	36	93	20	51	89	98	.007
Triglycerides	31	88	20	40	80	104	.002

[1] Level of significance of F-ratio for analysis of covariance.

SOURCE: Jenkins, C. D., et al. (*14*).

TABLE 10.—*Annual incidence rates of new coronary heart disease, by smoking habits, adjusted for age and seriatim, for specified other risk factors*

[Rates are annual incidence per 1,000 men, aged 50 to 59 years at entry into study]

Specified other risk factors	Never smoked	Former cigarette smokers	Pipe and cigar only	Daily cigarette consumption			p.[1]
				1–15	16–25	26 or more	
Cholesterol	115	142	153	115	211	264	0.154
Beta/alpha ratio	107	142	144	120	213	262	.127
Lipalbumin	109	140	151	122	218	262	.135
Systolic BP	118	127	144	129	211	266	.136
Diastolic BP	109	127	135	127	220	273	.066
Ponderal index	107	131	140	122	222	269	.084
Physical activity	113	142	149	115	213	249	.216
Amount of exercise	113	144	151	118	211	255	.203
Income level	113	138	147	120	220	258	.156
All of the above	113	118	138	140	213	258	.158
Triglycerides	113	147	144	80	195	260	.121

[1] Level of significance of F-ratio for analysis of covariance.

SOURCE: Jenkins, C. D., et al. (*14*).

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TABLE 11.—*Incidence of new coronary heart disease, by smoking category and behavior type, for men aged 39–49*

[Rates are age-adjusted annual incidence per 1,000 men]

Behavior type	Never smoked		Former cigarette smokers		Current and former pipe and cigar only		Daily cigarette consumption						Total	
							1–15		16–25		26 or more			
	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases
A	5.3	5	13.8	7	1.3	1	1.6	1	15.8	15	14.9	16	9.3	45
B	1.3	2	5.1	3	2.2	2	7.3	4	3.1	3	4.9	4	3.3	18
Total	2.9	7	9.1	10	1.8	3	4.9	5	9.3	18	10.4	20	6.2	63

SOURCE: Jenkins, C. D., et al. (*14*).

TABLE 12.—*Incidence of new coronary heart disease, by smoking category and behavior type, for men aged 50–59*

[Rates are age-adjusted annual incidence per 1,000 men]

Behavior type	Never smoked		Former cigarette smokers		Current and former pipe and cigar only		Daily cigarette consumption						Total	
							1–15		16–25		26 or more			
	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases
A	12.4	5	18.6	8	21.8	8	16.4	5	21.5	9	30.0	14	20.4	49
B	10.0	4	5.1	1	8.4	3	4.7	1	21.1	7	19.1	5	12.0	21
Total	11.1	9	14.2	9	14.9	11	11.5	6	21.3	16	26.0	19	16.8	70

SOURCE: Jenkins, C. D., et al. (*14*).

Epidemiological studies linking smoking and CHD have been carried out in various countries. In a retrospective study in Dublin, of 400 patients under the age of 65 who experienced myocardial infarction, Mulcahy, et al. (*18*) observed a definite association between smoking and the development of the disease.

A prospective epidemiological study of risk factors of CHD, in an Israeli population, indicates that smoking is associated with a higher risk of CHD (*17*).

In a retrospective study of 503 male patients with myocardial infarction and 714 age-matched controls in Munich, Schimmler, et al. (*22*) report that cigarette smoking plays a significant role as a risk factor.

A recent paper by Cederlof, et al. (*5*) employs the twin-study method on a population of American twins, using a similar approach to that previously employed in a Swedish twin population. The purpose is to compare the contribution of genetic and environmental influences to the development of angina pectoris. The authors imply that their study indicates a more important role for genetic factors than for smoking. However, this study can be criticized on several grounds. The authors based their detection of angina pectoris on the results of a self-administered questionnaire designed to elicit a history of chest pain of presumable cardiac origin; previous studies in Swedish twins have shown a low rate of clinical confirmation of heart disease in those classified positive by questionnaire. No data are available on the health and smoking habits of 58 percent of the original group or the 41 percent of the "eligible twin pairs" who were nonrespondents. The authors' definition of a present smoker includes persons who have stopped smoking cigarettes for up to 3 years and thus includes persons who in other studies have been classified as ex-smokers. This definition of a cigarette smoker might contribute to an underestimation of the immediate effect of current cigarette smoking, since an unstated number of recent ex-smokers are included in the same category as current cigarette smokers.

The relationship between cigarette smoking and the development of angina pectoris has not been clarified. However, Aronow, et al. (*1*) have shown that smoking one cigarette before exercising reduces the energy expenditure required for patients with classical angina pectoris to develop chest pain while exercising on a bicycle ergometer.

Atherosclerosis

A review of autopsy studies by Strong and Auerbach, suggesting that cigarette smoking has a chronic effect leading to advanced degrees of atherogenesis, was presented in the Health Consequences of Smoking, 1967 (*26*). Further studies have recently been published in this area.

Sackett, et al. (*21*) have demonstrated a clear dose-relationship between cigarette smoking and the severity of aortic atherosclerosis at autopsy. Their study of 1,019 consecutive autopsies, on patients who had been interviewed about their smoking habits prior to death, showed a significant increase in the severity of aortic atherosclerosis with increasing use of cigarettes, measured both by intensity and by duration of smoking.

An autopsy study from Russia by Avtandilov, et al. (*3*) demonstrated a significantly greater degree of atherosclerosis in the coronary arteries of smokers than in those of nonsmokers.

Viel, et al. (*28*) have reported on the severity of coronary atherosclerosis at autopsy of 1,150 men and 290 women who died violent deaths in Chile. Information on smoking habits was available on 566 men. The authors report no relationship between atherosclerotic lesions and the use of tobacco. The degree of atherosclerosis was expressed as the percentage of the surface of the intima of the left anterior descending coronary artery covered by fatty streaks and fibrous plaques. An examination of the data presented in graphic form indicates that the moderate and heavy smokers appear to show consistently higher percentages of diseased areas than the nonsmokers. But the statement of the authors implies that these differences were not statistically significant when subjected to an analysis of variance.

A study by Astrup was reviewed in the 1968 Report (*27*). This study showed that in rabbits on a high cholesterol diet, chronic carbon monoxide exposure has a marked atherogenic effect.

Kjeldsen, et al. (*15*) compared the vascular pathology in rabbits fed a high cholesterol diet and maintained in an hypoxic atmosphere (10 percent oxygen) with that in rabbits exposed only to the high cholesterol diet. The authors demonstrated that hypoxia leads to an increase in the degree of plaque formation in the coronary arteries and in the amount of visible aortic atheromatosis, as well as to an increase in the aortic content of cholesterol and triglycerides. In addition, the hearts of the hypoxic animals showed marked perivascular xanthomatosis, often infiltrating the surrounding myocardium. In summarizing this experiment and their previous findings of increased atheromatosis in hypercholesterolemic rabbits subjected to high carboxyhemoglobin (COHb) levels, the authors (*2*) state that tissue hypoxia seems to be an important factor in initiating these lesions, regardless of the manner in which the hypoxia is produced. Although the COHb levels in the rabbits and the degree of hypoxia were much higher than that experienced by human smokers, these results suggest a mechanism by which smoking might contribute to atherosclerosis.

Hass, et al. (*12*), extending studies reviewed in the 1968 Report (*27*), have demonstrated that the administration of injections of nico-

tine to hypercholesterolemic rabbits who are also given vitamin D enhances the peripheral atheromatous calcific arterial disease which is produced by the combination of hypercholesterolemia and vitamin D administration. The addition of nicotine to the regimen also resulted in the frequent occurrence of thromboarteritis in the distal calcified arteries of cardiac and skeletal muscle, and of the smooth muscle of the gastrointestinal tract. The nicotine effect was reproduced by substituting appropriate dosages of adrenalin for nicotine and abolished by adrenalectomy.

Lellouch, et al. (*16*) have reported that the administration of a mono-amine oxidase (MAO) inhibitor to rabbits on a regimen of daily nicotine injections significantly reduced the number of animals who developed fibrotic lesions of the aorta in response to nicotine. Further work is in progress to elucidate the mechanism of the MAO effect.

Evidence presented in this and previous reports suggests that cigarette smoking promotes atherosclerosis.

Thrombus Formation and Blood Flow

Hess, et al. (*13*) discovered aggregations of platelets, erythrocytes, fibrin, detached epithelial cells, and some as yet unidentified cells on the aortic and carotid walls of rabbits subjected to cigarette smoke.

The discovery of a plasma factor which increases the *in vitro* synthesis of fibrinogen by human liver biopsies has been reported by Pilgeram, et al. (*20*) in older patients who have recovered from myocardial infarction. This factor has been tentatively identified as free fatty acid (FFA). The authors state that the association between FFA and fibrinogen synthesis may provide the link between hyperlipemia and clotting. Cigarette smoking causes an increase in FFA through its stimulation of catecholamine release.

Several recent studies have begun to elucidate the role which changes in blood viscosity and certain features of the microcirculation might play in the development of atherosclerosis and coronary heart disease.

Dintenfass (*7*) has suggested that myocardial infarction and coronary thrombosis may be the result of a number of factors, separate or interrelated, all leading to a high viscosity of the blood. These factors may affect the migration and adhesion of platelets, the volume of plasma, and the rigidity of the red blood cell. Phenomena leading to high blood viscosity may occur in focal areas leading to occlusion of small vessels, resultant ischemia, and an infraction of either subclinical or catastrophic proportions, depending on the location and number of vessels involved. Dintenfass also believes that an increase in blood

viscosity precedes the clinical manifestations of the high blood viscosity syndrome and that the increased blood viscosity seen in post myocardial infarct patients is a reflection of the etiology rather than the effect of the disease.

Local hypoxia leading to an increase in the rigidity of the blood cell might be produced by cigarette smoking through the increase in COHb. Platelet adhesiveness is increased by smoking, probably secondary to the release of catecholamines (*27*).

In a study of 50 white males with myocardial infarcts and 40 controls, Stables, et al. (*23*) found that the patients with myocardial infarct had a mean hematocrit level significantly higher than that of the controls. Studies of blood volume indicated that a reduction in plasma volume rather than an increase in red cell mass among the myocardial infarct patients accounted for the elevated hematocrit.

Carbon Monoxide

Several reviews of the pathophysiology of exposure to carbon monoxide (CO) have appeared recently. These are pertinent to the discussion of the relationship of smoking to health, since cigarette smoke contains amounts of CO sufficient to cause a COHb level of 5 to 10 percent in the smoker, depending on the amount smoked and degree of inhalation (*9*, *10*).

Bartlett (*4*) has pointed out that because the absorption of CO from the ambient environment is dependent upon the concentration of CO in the environment as contrasted to that in the blood, smokers with a COHb level of 5 percent will not absorb CO from inspired air unless the concentration of CO in the air exceeds 30 parts per million. However, he also states that because the excretion of CO between cigarettes will be lower in CO polluted air, the smoker will have a higher long-term average COHb level in a polluted environment. Patients with heart disease may be particularly susceptible to the hypoxic burden caused by the presence of COHb.

Goldsmith, et al. (*10*) have stated that for the U.S. urban population, cigarette smoking is probably the most important cause of increased COHb above the endogenous level produced by heme catabolism, followed by automobile exhaust, occupational sources, and home heating and cooking devices, in that order.

Although Dinman (*6*) minimizes the importance of the effect of CO levels of 5 to 10 percent on the myocardium, he states that a shortcoming in his approach is that focal areas of myocardial ischemia are not reflected in the determination of oxygen saturation made from samples of blood taken from the coronary sinus. Such areas of ischemia might be important in initiating fatal arrhythmias. Levels of COHb

which decrease further the oxygen supply to the ischemic myocardium might be readily provided by cigarette smoking.

Eliot, et al. (*8*) have reported effects of cigarette smoking on the oxygen affinity of hemaglobin independent of the presence of CO. Their results suggest that cigarette smoking may have both acute and chronic effects on oxygen affinity which differ in direction. The authors caution, however, that the *in vivo* oxygen affinity of hemoglobin may be different from that implied by the static equilibrium data. Further research is in progress.

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CHAPTER 2

Smoking and Chronic Obstructive Bronchopulmonary Disease

Contents

SMOKING AND CHRONIC OBSTRUCTIVE BRONCHOPULMONARY DISEASE

Summary

Additional evidence which supports the previous judgment of a cause and effect relationship between cigarette smoking and chronic obstructive bronchopulmonary diseases, especially chronic obstructive bronchitis, continues to accumulate from both the United States and abroad. New work has been published in the past year which provides additional information on the possible mechanisms by which cigarette smoking can lead to the production of pulmonary emphysema. These mechanisms include collapse of small airways, changes in pulmonary surfactant, impairment of pulmonary clearance, disruption of the normal architecture of the bronchial epithelium, and obstruction of capillaries of the bronchi and alveoli. At present, there is no unified hypothesis for the pathogenesis of pulmonary emphysema; however, the pathogenetic mechanisms may involve more than one component of lung tissue. Epidemiological and laboratory evidence supports the view that cigarette smoking can contribute to the development of pulmonary emphysema in man.

Chronic Bronchitis

Cigarette smoking is the most important cause of chronic bronchitis. In the past year, studies from various countries have appeared in the literature reconfirming this association. In studies of populations of working men in Italy (*15*), the Netherlands (*6*), England (*16*, *35*) and the United States (*9*), smokers were found to have a significant increase in either incidence or prevalence of chronic bronchitis as compared to the nonsmokers. Studies of populations from rural and urban Sweden (*31*) and rural Australia (*25*) produced similar findings. A South African study (*45*) demonstrated decreased forced expiratory volumes (FEV_1) and peak expiratory flow rates (PEFR) with increased tobacco consumption, even in those who did not have chronic bronchitis.

Prevalance of Chronic Obstructive Bronchopulmonary Disease

The prevalence of chronic obstructive bronchopulmonary disease is probably underestimated. In a study of death certificates, Moriyama, et al. (*39*) have reported that chronic obstructive bronchopulmonary disease is often omitted as a contributing cause of death. Mitchell, et al. (*38*) also found that the disease often goes unreported. Barach, et al. (*5*) maintain that much of the reported increase in the prevalence of chronic obstructive bronchopulmonary disease can be accounted for by better diagnosis. However, Barach, et al. base their statement on the supposition that the rising death rates from chronic obstructive bronchopulmonary disease are incompatible with the fact that many people are giving up smoking. However, it should be pointed out that chronic obstructive bronchopulmonary disease associated with cigarette smoking may be the result of many years of exposure to cigarette smoke and the mortality rates from bronchitis and emphysema would not reflect large-scale smoking cessation for some time to come. Burrows (*10*) has pointed out that the effects of cessation of smoking on the course of already existing chronic obstructive bronchopulmonary disease may be difficult to assess, since it may be that those who are disabled by severe disease tend to stop smoking more often than those who have milder forms of the disease. The beneficial effects of cessation of smoking could thus be masked.

Pulmonary Emphysema

Many agents appear to contribute to the development of emphysema, but epidemiological and experimental evidence indicates that cigarette smoking is the most important agent in the development of pulmonary emphysema in man. Mention of the theories of pathogenesis of pulmonary emphysema, long the subject of debate among medical scientists (*1*, *34*, *46*, *47*, *48*), may help to serve as background for the presentation of recent research on the role of cigarette smoking in the development of emphysema.

Two major theories of the pathogenesis of chronic obstructive pulmonary emphysema have been proposed. One theory states that the primary lesion of emphysema is vascular and involves obstruction either by thrombosis or by endarteritis of the pulmonary or bronchial arterial branches. The resultant loss of nutrient supply is thought to result in ischemic necrosis of the alveolar wall and septa. The other major theory states that chronic obstructive pulmonary emphysema results from the direct effect of toxic inhalants on the pulmonary tissue, in the areas of the terminal bronchioles and alveoli. According to this theory, changes seen in the pulmonary and bronchial vessels are

secondary to the destruction of nonvascular tissue. It may well be that the pathogenesis of pulmonary emphysema can involve several mechanisms and that both of these theories may be applicable but not mutually exclusive (*44*).

Experimental Studies in Man

Anderson, et al. (*2*) have reported preliminary results which indicate that cigarette smoking causes acute changes in the ventilation/perfusion relationships of the lung and that patients with chronic obstructive bronchopulmonary disease appear to be particularly liable to these changes. In some patients the changes are predominantly in perfusion, a finding which lends support to the vascular theory of pulmonary emphysema. In other patients, the changes are predominantly in ventilation, a finding which lends support to the theory of the direct effect of inhalants in the pathogenesis of pulmonary emphysema.

Anthonisen, et al. (*3*) investigated pulmonary function in 10 male smokers with clinically mild chronic bronchitis, all of whom had smoked cigarettes for at least 20 years. Besides the usual pulmonary function tests, these investigators employed a technique for the assessment of regional pulmonary function using radioactive xenon. Despite the fact that overall pulmonary function was nearly normal in several patients, all had decreased ventilation and depressed ventilation/perfusion ratios in some lung regions, with the basal areas being those most commonly affected. The author suggested that significant disease in the peripheral airways may exist in patients whose chronic bronchitis is clinically mild and who show no present impairment of ventilatory capacity. The radioactive xenon test may reveal severe compromise of the overall gas exchange when usual studies of ventilatory capacity do not reveal impairment. These changes in the distal airways may become more significant clinically as the patient ages, since aging has been shown to be associated with a diminution in the compliance of the lung (*29*). Peters, et al.(*40*) have reported that the lower flow rates found among college students who smoke, especially at lower lung volumes, may reflect disease in the small airways. The diminution in flow in these subjects was approximately proportionate to the total lifetime number of cigarettes smoked.

Fullmer, et al. (*22, 23, 24*) have found a high prevalence of Curschmann's type spirals in the sputum of cigarette smokers. The easily recognized spirals consist of inspissated mucus and are casts of the lumens of small bronchioles. These spirals were found in the sputum of 23 of 24 cigarette-smoking women and in 97 of 100 cigarette-smoking men. The total number of spirals on four slides prepared for

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microscopic examination varied from 0 to 500. Six of 10 ex-smokers had spirals in their sputum, but the number of spirals was reduced to a total of 10 or less on four slides. A nonsmoking control group exposed to cigarette smoke at work showed a low prevalence of spirals, while a control group of nonsmokers not exposed to cigarette smoke at work showed no spirals in their sputum. Fullmer has suggested that Curschmann's spirals may play a role in the development of emphysema by producing obstruction at the bronchiolar level. The spirals may also allow prolonged contact between admixed inhalants including cigarette smoke and the bronchiolar walls. A study of the presence of spirals in the sputum of a group of nonsmoking asthmatic bronchitics would be useful in an attempt to determine whether the presence of spirals is a direct result of exposure to cigarette smoke, or is a characteristic of the sputum of bronchitics, whatever the cause of their bronchitis.

Studies in Animals

Frasca, et al. (*17*, *18*) have reported on electron microscopic observations of the bronchial epithelium of dogs exposed to cigarette smoke by active inhalation through a tracheostoma. The epithelium of a dog exposed to 44 days of smoking by methods previously described by Cahan, et al. (*11*) showed a proliferation of goblet cells and a partial loss of cilia in the surface lining cells. After 420 days of exposure to cigarette smoke, the number of cell layers in the epithelium was found to be twice that of the nonsmoking dogs. Goblet cells and ciliated columnar cells were no longer present; instead, the surface was lined with columnar and cuboidal cells with stubby projections in place of cilia. Mitotic figures were frequently observed in the basal cells. These findings may be relevant to carcinogenesis as well as to the development of chronic obstructive bronchopulmonary disease.

Tyler (*49*) and McLaughlin, et al. (*37*) have studied the physiology and morphology of pulmonary emphysema in the horse. The lung of the horse has been reported to be similar in subgross anatomy to that of man (*36*). They have studied both the spontaneous disease, one of the several causes of the syndrome known as "heaves," and a similar but not identical pulmonary disease induced by the injection of chlorpromazine or of styrene beads into the bronchial arterial circulation. Their findings of obstructive lesions in the bronchial circulation and of accompanying emphysematous changes in the pulmonary parenchyma provide indirect support of a vascular theory of emphysema. Ricketts, et al. (*41*) were unable to produce emphysematous lesions in sheep by occlusion of the bronchial artery; however, species differences in the distribution of this vessel may be an important factor

in both experimental and spontaneous disease. The bronchial artery in the horse is reported to supply the alveolar septa, whereas in the sheep it is reported to reach only as far as the terminal bronchioles (*36*).

A pulmonary disease similar histologically to pulmonary emphysema in man appears spontaneously in certain populations of rabbits (*12*). Boatman, et al. (*8*) have studied this disease by means of the electron microscope. Three of their findings which tend to support the theory that the disease is primarily vascular in origin are as follows: loss of capillary endothelium, partial or complete filling of the capillary lumens with collagen, and frequent recanalization of the damaged capillaries.

Freeman, et al. (*19*, *20*, *21*) have investigated the effect of chronic exposure of rats to varying concentrations of nitrogen dioxide (NO_2), a gas which is found in cigarette smoke and in industrially polluted air. These investigators showed that the exposure of rats over their lifetime of 2 to 3 years to concentrations of 2 (± 1) parts per million of NO_2 resulted in reduction in cilia of the bronchial epithelium, a reduction in normal exfoliation, and the appearance of unidentified crystalloid inclusions. Exposure for only 16 weeks to a higher concentration of 4 (± 1) parts per million led to hypertrophy of the epithelium of the terminal bronchioles. Rats exposed to concentrations varying from 10 (± 1) to 25 (± 2) parts per million of NO_2 developed large, heavy, nonedematous lungs accompanied by dorsal kyphosis. The increase in weight of the lung was shown to be caused by widespread hypertrophy of the respiratory epithelium, especially in the bronchioles closely associated with alveolar ducts and in the terminal bronchioles. Hypertrophy of the bronchial epithelium and accumulation of amorphous proteinaceus material, fibrin strands, and macrophages resulted in narrowing of the lumens of the terminal bronchioles at their junctions with the alveolar ducts. Focal hypertrophy of alveolar epithelium appeared to be associated with compression of alveolar capillaries. The airspaces of the lung were increased in volume.

Other investigators have also reported an increase in alveolar size in rodents exposed to NO_2. Blair, et al. (*7*) exposed mice to 0.5 parts per million of NO_2 for 6, 18, or 24 hours each day. The animals were exposed to NO_2 for periods varying from 3 to 12 months; the degree of change in the pulmonary histology appeared to increase with increased total length of exposure. Besides producing enlarged alveoli, exposure to NO_2 also produced early bronchiolar inflammation with a concomitant reduction in the size of the distal airways.

Other Studies

In a recent extensive review of the nature and role of pulmonary surfactant, Scarpelli (*43*) states that the lowering of surface tension produced by the action of cigarette smoke on surfactant may predispose to the development of emphysema.

Cigarette smoke contains powerful ciliostatic agents (*50*, *51*, *52*) which can interfere with pulmonary clearance. Components of both the particulate and the gaseous phases adversely affect ciliary activity. Dalhamn, et al. (*14*) have pointed out that in assessing the effect of one or another of the components of cigarette smoke on ciliary activity in various animal systems particular attention must be paid to the level of exposure, since at different dosages the particulate and gaseous phases have different relative effects on ciliary activity. Other recent work by Dalhamn, et al. (*13*) has further clarified the extent to which certain components of cigarette smoke are retained in the human lung and includes the observation that retention of gaseous components depends in part on adsorption of the gases on particulate matter.

Ballenger, et al. (*4*) have indicated that the *in vitro* ciliostatic effects of oxidized nicotine are enhanced by prior infection of the tissue explants with Influenza B Virus.

Holma (*30*) has reported that cigarette smoke has acute depressant effects on pulmonary clearance in living rabbits.

Recently, observations have been published on the metabolism and function of the pulmonary alveolar macrophage which, together with mucus transport, performs the function of ridding the lung of both inanimate particles and bacteria. Green (*27*) points out the importance of the alveolar macrophage in pulmonary clearance of infectious agents. He has also observed a deleterious dose-response effect of cigarette smoke on the phagocytic activity of the macrophage and suggests that this effect may be related to the development of chronic bronchopulmonary disease.

In another paper, Green (*26*) found that the cytotoxic activity of cigarette smoke on pulmonary macrophages may be inhibited by glutathione and cysteine. Izard (*32*) observed that the gaseous phase of cigarette smoke or one of its components, acrolein, inhibited the multiplication of cultures of *Dunaliella bioculata* and also observed that the addition of cysteine to the medium protected against these effects of acrolein.

Heise, et al. (*28*) have reported that rabbit pulmonary alveolar macrophages secrete lysozyme into a culture medium. Lysozyme may be active in the clearance of bacteria from the lung.

Roque, et al. (*42*) found a decrease in the activity of oxiodoreductases and hydrolases in the alveolar macrophages of smokers. They

also found that the reduction in these enzymes was directly proportional to the amount of stored fluorescent material present in the macrophages. This material is thought to originate in tobacco smoke. Roque, et al. suggested that the tobacco smoke may have induced abnormalities in the mitochondria of the macrophage.

Kilburn (*33*) theorizes that the pathogenesis of chronic obstructive bronchopulmonary disease is related to the failure of macrophages to be cleared from the alveoli and bronchioles because of impaction of mucus. He suggests that dissolution of the cells exposes the alveoli and bronchioles to damaging enzymes and to the phagocytosed particles contained in the macrophage.

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CHAPTER 3

Smoking and Cancer

Contents

SMOKING AND CANCER

Summary

Previous reports (*59, 60, 61*) have presented the evidence that cigarette smoking is a major cause of lung cancer and that cessation of cigarette smoking sharply reduces the risk of dying from lung cancer as compared to the risk taken by those who continue to smoke. Cigarette smoking was also shown to be a significant factor in the causation of cancer of the larynx. A strong association between various forms of smoking and cancers of the buccal cavity, pharynx, and esophagus was also shown. Data were presented which indicated that cigarette smoking was associated with cancer of the urinary bladder. Data were also presented which suggested that cancer of the kidney and pancreas may be related to cigarette smoking.

During the past year, both population studies and laboratory studies from various countries have added to the weight of the evidence linking smoking and cancer. A major study of histological changes in the larynx has demonstrated the higher risk of premalignant changes among smokers. More studies have been done to identify those substances in tobacco smoke which take part in carcinogenesis. New animal models for the experimental study of respiratory cancer, which may be helpful in elucidating the mechanisms of respiratory tract carcinogenesis, have been developed and refined.

Epidemiological Studies

It is interesting to note that epidemiological information on cigarette smoking and lung cancer, similar to that which has been collected in the United States and Western European countries, is now being reported from Eastern Europe and Africa as well.

Lung Cancer

In Norway, a study of histologically proven cases of lung cancer by Kreyberg demonstrated the low frequency of lung cancer among nonsmokers. The cases were collected between 1950 and 1964 from two hospitals and a diagnostic laboratory which service all parts of Norway. The author states that the population represented in this study is most probably geographically representative of the whole country. In comparing his results in Norway with those in other European

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countries, Kreyberg stated that a nonsmoking Norwegian population today should present lung cancer cases in the same number, with the same sex ratio, and with the same representation of histological types as prevailed in Norway 40 years ago, and in Europe in general at the beginning of this century (*24*, *25*). The risks of developing various histological types of lung cancers among smokers, as contrasted to nonsmokers, are presented in table 1. Two facts are strikingly apparent from the table. First, the preponderance of the higher risk of lung cancer in smokers lies in the categories of epidermoid carcinoma and anaplastic small cell carcinoma. Second, while female smokers have a higher risk of developing lung cancer than female nonsmokers, the relative risks are smaller than those for males. At least part of this difference may be accounted for by differences in smoking habits between men and women. Women tend to smoke fewer cigarettes, to smoke brands lower in tar and nicotine, inhale less and smoke less of each cigarette than do men; therefore, women have lower exposure to cigarette smoke.

TABLE 1.—*Tumor prevalence among males and females 35–69 years of age, by type of tumor and smoking category*

[Smokers constituted 85 percent of populations studied]

Sex and type of tumor	Smoking category			Expected number among smokers[1]	Risk ratio among smokers
	Total	Smoking all methods	Non-smokers		
Males:					
Epidermoid carcinoma	434	431	3	17.0	25.4
Small cell anaplastic carcinoma	117	116	1	5.7	20.4
Adenocarcinoma	88	83	5	28.3	2.9
Bronchiolo-alveolar carcinoma	----	----	----	------	----
Carcinoid	46	39	7	39.7	1.0
Bronchial gland tumor	----	----	----	------	----
Total	685	669	16	90.7	7.4
Females:					
Epidermoid carcinoma	12	9	3	.75	12.0
Small cell anaplastic carcinoma	8	5	3	.75	6.6
Adenocarcinoma	56	14	42	10.5	1.3
Bronchiolo-alveolar carcinoma	----	----	----	------	----
Carcinoid	32	7	25	6.3	1.1
Bronchial gland tumor	----	----	----	------	----
Total	108	35	73	18.3	1.9

[1] Number that would be expected if incidence rate among smokers was equal to that of nonsmokers.

SOURCE: Kreyberg, L. (*24*).

Brett, et al. (*8*) found that the mortality rate for lung cancer in smokers in England was especially high for the smokers who "drooped" the cigarettes off the lip while they smoked, a habit which may result in the delivery of a greater dose of smoke from each cigarette.

Gelfand, et al. (*19*) in a study of lung cancer in Rhodesian Africans, reported a preponderance of smokers among the lung cancer patients as compared to a control group. The authors express the opinion that air pollution does not play a role in respiratory cancer in Rhodesia.

In the 1967 Health Consequences Report (*59*), it was pointed out that the lung cancer risk of ex-smokers declined, relative to those who continued to smoke. It equalled that of nonsmokers about 10 years after stopping smoking, and the rate of decline depended on the number of cigarettes previously smoked and the duration of smoking. Bross, et al. (*10*) reported that the risk of developing lung cancer is lower among filter cigarette smokers than nonfilter cigarette smokers. Since filter cigarettes are generally lower in tar content than nonfilter cigarettes, this study supports the inference that the tar content of cigarettes is a meaningful measure of exposure to risk.

In view of the fact that practically all lung cancer patients started to smoke nonfilter cigarettes and have smoked filter cigarettes only in recent years and for a variable length of time, a more exact comparison of the risks run by smokers of filter and nonfilter cigarettes must await further studies (*67*).

The relationship of smoking to lung cancer in women is an area of continuing concern, since we may expect a continued increase of lung cancer in women with the increase in cigarette smoking among them since World War II. Lombard, et al. (*32*) show a relationship of cigarette smoking to epidermoid lung cancer in women but not to adenocarcinoma. It is generally agreed that the contribution of cigarette smoking to the development of epidermoid and oat-cell lung cancer (Kreyberg Group I) in males is significantly greater than to the development of adenocarcinoma (Kreyberg Group II).

An association of other diseases to cancer of the lung is found in a report by Salzer, et al. (*48*). Salzer and his colleagues have reported in an autopsy study that lung cancer and scars from stomach ulcers are statistically associated and suggested that cigarette smoking may have contributed to both conditions. A study by Stamler, et al. (*53*) indicated that male cigarette smokers with elevated cholesterol levels had higher rates of lung cancer than those with lower cholesterol levels. Additional studies are needed to confirm and elucidate these observations.

Programs have been recently established to perform cytological examinations on the sputum of smokers, since they represent a population at a high risk for the development of carcinoma of

the lung. These programs have detected individuals with atypical or frankly malignant cells in their sputum before a shadow has appeared in the lung fields of x-ray (*18*, *62*). Valaitis, et al. (*62*) reported that some degree of cytological abnormality was found in the sputum of 4.8 percent of the smokers and 0.9 percent of the nonsmokers.

Oral Cancer

In the Soviet Union, Orlovskiy has shown an association between cigarette smoking and lung cancer, as well as an association between the use of "nas" (a mixture of tobacco and ashes) and the development of cancer of the oral cavity (*37*). Other studies of interest from around the world include one by Pindborg, et al. (*39*) on the epidemiology and histology of oral leukoplakia and leukoedema among Papuans and New Guineans. They report that smoking may be more closely associated with these conditions than is the chewing of betel nut which previously was considered the obviously associated habit. A study by Wahi (*64*) reports on the relationship of tobacco chewing to oral and oropharyngeal cancer in a district in India. Pindborg also presents evidence from India indicating that oral submucous fibrosis (*38*) may be associated with tobacco use and may result in an oral epithelium more susceptible to the carcinogenic substances in tobacco. In a study of oral malignancies indexed in a large tumor registry in California, Chierici, et al. (*13*) found that 88 percent of the cancer patients were smokers. The proportion of smokers ranged from 81 to 83 percent for cancers of the gingival and alveolar mucosa, buccal mucosa, hard palate, and lip, to 94 percent or more for cancers of the floor of the mouth, soft palate, tonsil, or oropharynx. Unfortunately, comparable percentages of smokers in a control population are not presented. No new studies have appeared which clarify the relative contributions of other environmental risk factors for oral cancer, such as alcohol consumption, nutritional problems, and poor oral hygiene.

Laryngeal Cancer

Auerbach, et al. (*1*) studied the histology of the larynx of 942 men, aged 21 to 95, who were autopsied at a single hospital between 1964 and 1967. Cases of primary cancer of the larynx were excluded from the study. Smoking histories for all cases were obtained from family members of the deceased by trained interviewers. The numerous randomized histological sections were graded by one observer. Table 2 shows the percentage of cells with atypical nuclei found in the true vocal cord. Of the men who never smoked, 75 percent had no cells with atypical nuclei, only 4.5 percent had sections with areas containing 60 to 69 percent of cells with atypical nuclei, and none had a higher percentage.

TABLE 2.—*Number and percent distribution by relative frequency of atypical nuclei among true vocal cord cells, of men classified by smoking category*

[100 per cent atypical cells defined as carcinoma]

Percent atypical nuclei	Never smoked regularly		Ex-cigarette smokers		Cigar/pipe smokers		Current cigarette smokers					
							Less than 1 pack a day		1–2 packs a day		2 or more packs a day	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Total	88	100.0	116	100.0	94	100.0	125	100.0	329	100.0	190	100.0
None	66	75.0	86	74.1	1	1.1	1	.8	0	-----	0	-----
Less than 50	8	9.1	14	12.1	4	4.3	25	20.0	4	1.2	0	-----
50–59	10	11.4	13	11.2	50	53.0	54	43.2	87	26.4	29	15.3
60–69	4	4.5	1	.9	23	24.5	21	16.8	116	35.3	75	39.4
70–79	0	-----	2	1.7	9	9.6	9	7.2	44	13.4	38	20.0
80–89	0	-----	0	-----	2	2.1	2	1.6	19	5.8	11	5.8
90–99	0	-----	0	-----	1	1.1	0	-----	5	1.5	0	-----
100:												
Carcinoma *in situ*	0	-----	0	-----	3	3.2	13	10.4	52	15.8	35	18.4
Invasive carcinoma	0	-----	0	-----	1	1.1	0	-----	2	.6	2	1.1

SOURCE: Auerbach, O., et al. (*1*).

The 116 ex-smokers had laryngeal histology similar to that of the nonsmokers, as far as atypical nuclei were concerned. However, disintegrating nuclei were found in 40.5 percent of the ex-cigarette smokers and in only 0.4 percent of the remaining cases. Only one of the 94 cigar and/or pipe smokers had no atypical cells. Three had carcinoma *in situ* and one case had a section showing early invasive primary carcinoma. The highest percentage of atypical cells was found among the cigarette smokers. The proportion of cases with a high degree of cellular change increased with increased daily smoking. None of the pack-or-more-a-day smokers was free of atypical nuclei. Of those who smoked two or more packs per day, 85 percent had lesions with 60 percent or more atypical cells as compared to 4 percent of the nonsmokers. Between 10 and 18 percent of the cigarette smokers had areas of carcinoma *in situ*, and four of the 644 cases showed early microscopic invasion. The thickness of the basal level of the true vocal cord was also directly related to the amount smoked (table 3).

TABLE 3.—*Number and percent distribution, by highest number of cell rows in the basal layer of the true vocal cord, of men classified by smoking category*

Number of cell rows	Never smoked regularly		Ex-cigarette smokers		Cigar/pipe smokers		Current cigarette smokers					
							Less than 1 pack a day		1–2 packs a day		2 or more packs a day	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Total	88	100.0	116	100.0	94	100.0	125	100.0	329	100.0	190	100.0
Less than 5 cell rows	30	34.1	7	6.0	4	4.3	3	2.4	1	0.3	0	-----
5 cell rows	29	33.0	27	23.3	20	21.3	27	21.6	38	11.6	20	10.5
6 cell rows	8	9.1	15	12.9	15	6.0	25	20.0	51	15.4	24	12.6
7 cell rows	6	6.8	12	10.3	18	19.1	12	9.6	38	11.6	19	10.0
8 cell rows	8	9.1	14	12.1	9	9.6	13	10.4	30	9.1	23	12.1
9 cell rows	1	1.1	7	6.0	7	7.4	6	4.8	26	7.9	14	7.4
10 or more cell rows	6	6.8	34	29.4	21	22.3	39	31.2	145	44.1	90	47.4

SOURCE: Auerbach, O., et al. (*1*).

Cancer of the Urinary Bladder and Kidney

Several studies have dealt with the relationship of smoking to cancer of the bladder and kidney. James, et al. (*23*) demonstrated that an association existed for cancer of the bladder. The study by Fraumeni (*17*) also showed epidemiological evidence for such a relationship for bladder and kidney cancers. Bennington, et al. (*3*, *4*) indicated an association between all kinds of tobacco usage and adenocarcinoma of the kidney as well as adenoma of the kidney. However, on the basis of this study alone, the relationship between "all kinds of tobacco" and cancer of the kidney cannot be considered as established in view of the small number of cases involved. In a preliminary report of a study on the epidemiology of cancer of the kidney, Wynder, et al. (*68*) have shown a strong association between excessive cigarette smoking and adenocarcinoma of the kidney, and although the disease is not uncommon in nonsmokers, they considered excessive cigarette smoking to be a contributory factor. This study found no relationship to pipe smoking, and only a very weak relationship to cigar smoking. A significant association was found between cigarette smoking and epidermoid cancer of the kidney, a relatively uncommon type of cancer. Further research on the strength and mechanisms of the association between smoking and cancers of the urinary tract is needed.

Cancer of the Pancreas

The previously suggested association between cigarette smoking and cancer of the pancreas was again noted in a Japanese study by Ishii, et

al. (*22*), in which the authors reported a higher relative risk for pancreatic cancer among smokers than among nonsmokers.

General Aspects of Carcinogenicity

The majority of the tumorigenic agents in tobacco smoke are found in the particulate matter "tar." The well established carcinogenicity of tobacco "tar" in a variety of animal species and tissues (*66*) was reconfirmed recently (*11*, *35*, *40*, *52*, *56*). A small portion of the smoke particulates (0.03 percent) is made up of polynuclear aromatic hydrocarbons (PAH) with two or more rings. A concentrate containing polynuclear aromatic hydrocarbons and amounting to 0.6 percent of the whole "tar" was found to be the most carcinogenic fraction of tobacco smoke (*66*). Another preparation of a PAH concentrate induced significant cytologic changes in mouse trachea and human fetal lung when grown in organ culture (*28*, *29*). Other applications of concentrations of selected polynuclear aromatic hydrocarbons have produced similar results (*27*).

Of the identified PAH, at least 12 are known tumor initiators. These particular compounds have been shown to be carcinogenic, even when applied in doses of a few micrograms (*63*, *66*). Tumor initiators induce changes in the target cells, especially in DNA (*9*, *14*). Tumor promoters are agents which promote the neoplastic transformation of initiated cells. Although the structures of most of these tumor promoters are still unknown, there appear to be several different types in tobacco smoke (*5*, *41*, *59*, *66*). Recently, Bock, et al. (*6*) published data which confirmed earlier findings that whole cigarette tar, the neutral fraction, two neutral subfractions and the weak acidic (phenolic) fraction contain tumor promoters. One recent study indicated that "tar" obtained from tobacco stems only had essentially no tumor promoting activity (*65*).

During the last year, several studies have reconfirmed the finding that selection of tobacco and the use of tobacco sheets and filters can lead to a significant reduction of "tar" and PAH in cigarette smoke, as well as to a reduction of the tumorigenicity of tobacco "tars." Similar results have also been reported for commercial cigarettes (*21*, *34*). Experimental studies demonstrated that with tobacco additives one can reduce "tar," nicotine, PAH and tumorigenicity of cigarette smoke (*12*, *21*). In terms of selective reduction of tobacco smoke components, these investigations may be of practical value, as well as of academic interest (*57*).

Tobacco Alkaloids

Present evidence does not indicate that tobacco alkaloids are carcinogenic. A possible exception may be cotinine, which was reported to induce malignant tumors in rats [principally leukemias (*58*)] and

adenomas of the bladder in mice (*7*). Boyland recently suggested that one or more of the three possible nicotine-N-oxides may be present in tobacco smoke and may be carcinogenic (*7*).

Tobacco alkaloids could theoretically contribute to the overall carcinogenicity of tobacco smoke, based on the possibility that in tobacco smoke nornicotine and other secondary amines may react with nitrogen oxides to form the N-nitrosamines, of which several are known carcinogens, especially N-nitrosonornicotine and N-nitrosoanabasine (*36*). So far, however, N-nitrosamines of nornicotine and other alkaloid N-nitrosamines have not been detected in tobacco smoke (*36*).

Nickel

The relationship of nickel compounds to the development of cancer has been discussed in a recent review by Sunderman (*55*), who suggests that there is a possibility that nickel carbonyl may be present in cigarette smoke and may act as a cocarcinogen by inhibiting the induction of pulmonary benzopyrene hydroxylase, an enzyme which converts 3,4-benzpyrene to noncarcinogenic hydroxylated derivatives.

Experimental Aspects of Carcinogensis

Retention of Smoke Constituents

Studies on human smokers by Dalhamn, et al. (*15*) demonstrated that about 60 percent of the volatile, water soluble compounds of cigarette smoke, 20 percent of the volatile, nonwater soluble compounds, and 16 percent of the particulate matter of cigarette smoke can be retained in the mouth when the smoke is held in the mouth for up to 2 seconds. Under conditions in which the smoke is immediately deeply inhaled, between 91 and 99 percent of the components of cigarette smoke investigated (particulate matter, toluene, acetonitrile, acetone, isoprene, acetaldehyde) were retained, with the exception of carbon monoxide, of which 50 to 60 percent was retained (*16*).

Changes in Cell Cultures Induced by Cigarette Smoke

Leuchtenberger, et al. (*30*) have reported that passing cigarette smoke through a charcoal filter prevented the damage caused by either whole smoke, or the isolated gas phase of cigarette smoke, to cultures of mouse kidney cells. In the same paper, they reported that the single exposure of tissue cultures to puffs of charcoal-filtered smoke produced a significant increase in the mitotic index of the kidney cells. In another study, Leuchtenberger, et al. (*31*) reported that single exposure to nine puffs of the gas phase from charcoal-filtered cigarette smoke quickly stimulated the synthesis of DNA and RNA by cultures of mouse fibroblasts. Repeated exposure of the cultures to the filtered gas phase resulted in morphological and cytochemical changes indicative

of abnormal proliferation. Since the same alterations were found to be present, to a much lesser extent, in some control cultures, the authors considered that the filtered gas phase enhanced characteristics already possessed by the cells. They concluded that the gas phase of unfiltered cigarette smoke contains not only substances which inhibit cellular metabolism, but also factors which stimulate cellular metabolism. These latter factors may be unmasked by passing the gas phase through a charcoal filter. The identities of the specific gases removed by the charcoal filter and the extent to which each was removed were not reported by the authors. Investigation of the relationship between the changes observed in the tissue cultures and *in vivo* metabolism is necessary for the interpretation of the results of these experiments.

Experimental Studies of Bronchogenic Carcinoma in Animals

Because of the technical problems involved in inhalation experiments in small animals (*59*, *61*), various animal models have been developed which do not employ the inhalation of smoke. These models have been used to study the role played by carcinogenic substances found in tobacco smoke in the induction of bronchogenic carcinoma.

Saffiotti (*43*) in a recent review of experimental respiratory tract carcinogenesis described the development of experimental models for the induction of pulmonary tumors and discussed a method of inducing bronchogenic carcinomas in Syrian golden hamsters by intratracheal instillation of a finely particulated crystalline carcinogen (e.g., benzo(a)pyrene) attached to a suspension of fine particles of a carrier dust (e.g., ferric oxide). This method reproduces some of the conditions of human exposure to inhaled carcinogens and has resulted in incidences of up to 100 percent of respiratory tumors, mostly squamous cell and anaplastic carcinomas of the larger bronchi. These tumors have been found to be invasive, metastasizing, and transplantable. Saffiotti reported that the carrier dust particles play an essential role in transporting the carcinogens through the bronchiolar and alveolar wall into the lung tissues where they are phagocytized. The carcinogens are then eluted by the plasma and diffused into the lung tissue, reaching up to the mucosa of the larger bronchi (*42*, *44*, *45*, *46*). Variations in particle size and distribution in the suspended particulate matter affect the retention rates of benzpyrene in the lungs (*47*). The development of this experimental model has led to the undertaking of new research in many laboratories attempting to define the factors responsible for carcinogenesis in the respiratory tract.

Two other techniques used to produce squamous cell carcinoma in small laboratory animals are the passage of threads impregnated with carcinogenic hydrocarbons into the lung and the implantation of wire

mesh pellets in the bronchus. The latter technique gives a dose-response relationship between carcinogenic hydrocarbons and squamous cell carcinoma of the lung in rats (*27*). In order to overcome the traumatic effects of the surgery involved in these procedures, two additional techniques have been utilized. In one method, the carcinogen is suspended in Freund's adjuvant and upon tracheal instillation can lead to bronchial cancer (*69*). In this experiment, even more cancers were found when the rats were pretreated with tubercle bacilli. Pretreatment of the animals with tubercle bacilli produced infarcts, as well as scarring of the lung. This finding is of interest because earlier studies showed that scarring of rat lung by the halogenated hydrocarbon hexachlorotetrafluorobutane increases their susceptibility to the development of squamous carcinoma when exposed to carcinogenic hydrocarbons (*54*). That scarring of the lung may increase the susceptibility of the lung to carcinogens is in line with some recent observations on humans by Bennett, et al. (*2*) who showed the frequent occurrence of pulmonary scars in males with adenocarcinoma of the lung.

Experimental Aspects of Cancer of the Bladder and Kidney

Tobacco smoke appears to contain traces of several aromatic amines which are established bladder carcinogens. Of these, however, only Betanaphthylamine has thus far been identified in tobacco smoke with 2.2×10^{-8} g. per cigarette (*20*). At concentrations such as this, it appears unlikely that such aromatic amines can account for the increased risk among cigarette smokers of developing kidney and bladder cancer. A more likely correlation may exist between these types of cancers in smokers and their elevated urinary excretion rate of carcinogenic metabolites of tryptophan, and their oxidation products (*49, 50*).

Recently, the tobacco alkaloid cotinine was reported to induce adenomas in the bladder of mice [16 percent (*7*)]. This observation needs further testing. Cotinine is one metabolic product of nicotine and is found in tobacco, cigarette smoke (*26*) and the urine of smokers (*33*).

A study by Schlegel, et al. (*51*) indicates an elevated concentration of certain o-aminophenols plus their phenoxazon-oxidation products in the urine of certain types of bladder cancer patients and cigarette smokers, when compared to the urine of nonsmokers. Further studies are needed on this problem.

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CHAPTER 4

Effects of Smoking on Pregnancy

Contents

EFFECTS OF SMOKING ON PREGNANCY

Summary

Maternal smoking during pregnancy is associated with decreased infant birth weight and increased incidence of prematurity, as defined by weight alone, and may be associated with an increased incidence of spontaneous abortion, stillbirth, and neonatal death. Changes in the metabolism of the placenta and in various hematological factors in the newborn infant have been found to be associated with maternal smoking, but the mechanism of the effect of smoking on the outcome of pregnancy remains to be determined.

New studies on the effect of maternal smoking on the outcome of pregnancy have been published since the review of this topic in the 1967 Report (*11*). In the 1967 review, the literature cited supported a relationship between maternal smoking and low birthweight and prematurity in infants. However, the evidence relating the maternal smoking to fetal or neonatal death was not definitive. The addition of new studies has reconfirmed the relationship between maternal smoking and low birth weight and prematurity. The relationship between maternal smoking and spontaneous abortion, stillbirth, and neonatal death has been investigated in several studies. As detailed below, some of the studies reported a statistically significant increase in unsuccessful pregnancies in mothers who smoked when compared with mothers who did not smoke.

Epidemiological Studies

In a prospective study of more than 2,000 pregnant women, Russell, et al. (*8*) examined the effect of the mother's smoking habits and blood pressure on the outcome of the pregnancy and on the birth weight of the infant. A smoker was defined as one who regularly smoked five or more cigarettes a day. In each blood pressure category, the percentage of unsuccessful pregnancies (abortion, stillbirth, neonatal death) was higher for smokers. Although fewer smokers were found in the higher blood pressure categories, women who smoked and had blood pressure levels equal to, or greater than, 150/100 had a rate of unsuccessful pregnancy of 31.4 percent as compared to a rate of 14.5 percent among nonsmokers with the same blood pressure

levels. Although the number of women in the two groups was small (35 and 138, respectively), the difference observed was statistically significant. For those with blood pressure levels of less than 140/90, the percentage of unsuccessful birth was 6.5 among smokers and 2.7 among nonsmokers; for those with blood pressure levels in the range of 140/90, the percentage was 6.8 among smokers and 4.1 among nonsmokers.

Extrapolating from his series, Russell (*7*) estimated that one out of every five unsuccessful pregnancies in women who smoked regularly would have been successful if the mother had not smoked regularly during the pregnancy. This statement implies a cause-and-effect relationship between maternal cigarette smoking during pregnancy and abortion and perinatal death. In the absence of proof of a cause-and-effect relationship, the least that can be said is that on the basis of the findings of Russell, et al., one out of every five unsuccessful pregnancies among women who smoke regularly during pregnancy would not have been unsuccessful if these women had the same risk of unsuccessful outcome of pregnancy as women who do not smoke.

In keeping with previous findings, Russell, et al., found that the mean birth weight of the infant was lower for the smoking mothers in each blood pressure category. Various factors were examined as confounding variables for their possible effect on birth weight and the production of spurious associations. These included: social class of consort, maternal age, parity, maternal height, social class of woman's father, educational level, age of consort, maternal attitude toward the pregnancy, work during pregnancy, and sex of offspring. For each variable, the smoking effect was clearly distinguished as a separate effect even when the individual factor was itself associated with smoking (consort's social class, father's social class, and maternal educational level).

A study of increases in the infants' weight and in their head circumference during the early weeks of life revealed that the babies of smoking mothers grew faster than those of nonsmokers through the sixth month after birth. However, the mean weight per week of conception age (duration of pregnancy, plus age after birth) was greater in babies of nonsmokers through the sixth week after birth, the effect not being visible at the sixth month examination. These last two findings support the theory that smoking during pregnancy acts as a retarding influence on fetal growth and that a catching-up phenomenon begins among the babies of smoking mothers at birth when the toxic influence is removed.

In a controlled study of 197 premature births among Negroes, Terris, et al. (*9*) found a significantly higher prevalence of smoking among the mothers of premature infants. Prematurity was defined as a birth weight of 2,500 grams or less.

Mulcahy, et al. (*6*) studied the relationship between smoking habits and the outcome of pregnancy in 3,681 women admitted to the Coombe Lying-in Hospital in Dublin, Ireland. Besides finding significantly lower birth weight for infants born to mothers who smoked, they discovered a significant increase in the incidence of neonatal death, stillbirth, and spontaneous abortion. These effects were independent of age or parity. No significant difference in the rate of congenital abnormalities was found between the offspring of the smokers and those of the nonsmokers.

Kizer (*4*) studied the effect of maternal smoking on the outcome of pregnancy in 2,095 patients in Venezuela. He found a significant diminution in the birth weight of infants of smoking mothers and a higher incidence of premature rupture of the membranes, but did not find a difference in the incidence of abortion or perinatal mortality.

Duffus, et al. (*2*) studied the relationship between smoking during pregnancy and the incidence of albuminuric preeclamptic toxemia in 2,543 married, urban primigravidae attending antenatal clinics in Aberdeen in 1960. Albuminuric preeclampsia is defined as albuminuria in pregnancy in which the urine contains at least 0.25 grams of albumin per liter accompanied by a rise in diastolic blood pressure to 90 mm Hg. or more, on 2 or more days after the 26th week of gestation or progressively during labor. The incidence of albuminuric preeclampsia was lower in smokers than in nonsmokers. Among the preeclamptics, however, smokers lost more babies in the perinatal period than the nonsmokers. The babies of smokers, both normal and preeclamptic, had a lower mean weight than the babies of nonsmokers. In the preeclamptic group, a greater percentage of the babies of smokers weighed less than 5 pounds. These differences are in keeping with those found in other studies but do not reach statistical significance. The implication is that smoking mothers are less likely to be preeclamptic, possibly by way of blood pressure effects, but are more likely to have their pregnancies result in perinatal death in the event they are preeclamptic.

In a study of 5,843 deliveries in Hungary, Fülöp (*3*) found a statistically significant increase in premature births among women who smoked during their pregnancies, whether the women were married or unmarried, held a job, or were unemployed. Lacuska, et al. (*5*) found a higher frequency of premature births and abortions among women who smoked during pregnancy than among nonsmokers, although the differences fell short of statistical significance.

Tokuhata (*10*) analyzed the fertility history in relation to smoking in groups of married women who died of breast cancer, genital cancer, and various noncancerous diseases. Statistically significant increases in both the rate of infertility (as judged by absence of preg-

nancy) and in fetal loss (defined as abortions and stillbirths) were found in smokers who died of noncancerous diseases. These differences withstood analysis for a number of possible confounding factors. However, since the sample was made up of women who died in a certain geographical area in a given amount of time, biases may have been introduced. Retrospective findings in a group of dead people are not necessarily the same as findings derived in a prospective study of a living population.

Although by this time the evidence for reduction in birth weight of babies born to smoking mothers is overwhelming, a problem that remains to be solved is why some studies do and others do not appear to show fetal wastage as measured by abortion, stillbirth, and neonatal death. It may be that the method of selection of the population under study, especially the degree to which entire obstetrical histories are included, accounts for this variation.

Experimental Studies

Younoszai, et al. (*13*) compared various hematological factors in the blood of 16 smoking mothers and newborn infants with those of 16 nonsmoking mothers and their offspring. Both groups of infants were delivered at term and appeared clinically well. The smoking mothers had a mean carboxyhemoglobin saturation of venous blood of 8.3 percent as compared to 1.2 percent in the nonsmoking mothers. Corresponding figures for the umbilical vein cord blood were 7.3 percent and 0.7 percent. A mild metabolic acidosis was seen in the infants of smokers. These infants also had a higher mean capillary hematocrit than those of the nonsmoking mothers. The authors point out that the differences, although real, probably are not of clinical significance in the newborn. However, the effect of chronic exposure of the embryo and fetus to carboxyhemoglobin levels and other hematological abnormalities has not been elucidated.

Welch, et al. (*12*) reported that the placentas from women who smoked during pregnancy show a much greater ability to hydroxylate benzo(a)pyrene than the placentas from women who did not smoke during pregnancy. The placentas from women reporting similar cigarette consumption varied greatly in the degree of BP hydroxylase activity. However, no information is available on the brand of cigarettes smoked or the degree of inhalation, differences which may result in different dosages of BP. It is possible, but not likely, that carcinogens in tobacco smoke reach the fetus in significant amounts. The ultimate effect of the exposure of the human fetus to carcinogenic substances is unknown.

Becker, et al. (*1*) studied the effect of subcutaneous injections of increasing doses of nicotine on groups of pregnant rats and their off-

spring. They found that the rats receiving nicotine injections consumed less food and gained less weight than control animals and that the magnitude of this effect increased when the dose of nicotine was greater. Whereas no other differences were found in the rats receiving lower dosages, those receiving 3.0 mg./kg. or 5.0 mg./kg. daily had offspring which differed from those of the controls in being lighter, having a longer gestation, a higher mortality rate during the first 48 hours of life, and a fetal appearance.

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CHAPTER 5

Smoking and Noncancerous Oral Disease

Contents

SMOKING AND NONCANCEROUS ORAL DISEASE

Summary

The previous reports have not presented findings on noncancerous oral disease. Several recent studies have made a review appropriate at this time. This review of the available literature leads to the conclusion that ulceromembranous gingivitis, alveolar bone loss, and stomatitis nicotina are more commonly found among smokers than among nonsmokers. The influence of smoking on periodontal disease and gingivitis probably operates in conjunction with poor oral hygiene. In addition, there is evidence that smoking may be associated with edentulism and delayed socket healing. While further experimental and clinical studies are indicated, it would appear that nonsmokers have an advantage over smokers in terms of their oral health.

Epidemiological and Clinical Studies

Periodontal disease is a chronic destructive process affecting the supporting structures of the teeth (gingiva, periodontal fibers, and alveolar bone). It is generally considered inflammatory in nature. Solomon, et al. (*21*) studied data on 3,552 nonsmokers and 3,639 smokers, all white and between the ages of 20 and 79. He found that periodontal disease occurred without significant statistical difference in male and female nonsmokers of the same age, but that smokers of both sexes had a higher prevalence of the disease. The prevalence in female smokers paralleled that in male smokers in the younger age groups but resembled that of the nonsmokers in the older age groups. The authors believe that this difference is related to increased smoking in younger women.

Brandtzaeg, et al. (*3*) examined 206 Norwegian Army recruits between the ages of 19 and 25 and found a trend toward increased periodontal disease with increased smoking. However, when an analysis of covariance was performed, most of the changes in periodontal disease severity were accounted for by changes in oral hygiene. This finding suggests that tobacco consumption may influence the periodontal tissues but only with accompanying changes in oral hygiene.

A seemingly contradictory paper reporting on periodontal diseases in 8,206 Ceylonese was published by Waerhaug (*25*). He found tobacco smokers to have less periodontal disease than nonsmokers. He

pointed out, however, that for many individuals the alternative to smoking tobacco is chewing betel nuts, which is associated with even more periodontitis than cigarettes. Thus, tobacco users are relatively better off.

The relationship of smoking to gingivitis, the initial stage of periodontal disease, has also been studied. Arno, et al. (*2*) examined 1,346 employees of a manufacturing company in Oslo and found that tobacco smoking was associated with an increase in the prevalence of gingivitis. However, its importance as compared with that of oral hygiene was not a dominating one. Ludwick, et al. (*15*) studied 2,577 naval enlistees at the Great Lakes Naval Training Center and found no relationship between smoking and simple marginal gingivitis, but a significant one between smoking and ulceromembranous gingivitis (necrotizing ulcerative gingivitis, Vincent's gingivitis, trenchmouth). This is an acute form of periodontal disease of apparent sudden onset, characterized by ulceration of the tips of the interdental papillae, gingival bleeding, pain, and foul odor. In the United States and Europe, it occurs primarily in adolescents and young adults. Bacteria, local factors, systemic factors, and psychogenic factors have been suggested as contributing to its etiology (*10*).

Pindborg's study (*17*) of 1,433 Danish Royal Marines between the ages of 16 and 28 revealed that the prevalence of chronic marginal gingivitis was not affected by smoking, but that the prevalence of ulceromembranous gingivitis was much greater in smokers than nonsmokers. A second study by Pindborg (*16*) of 3,505 Danish military personnel confirmed these findings: nonsmokers had a prevalence of ulceromembranous gingivitis of 2.2 percent, while for those who smoked 10 g. or less of tobacco daily, the prevalence was 7.0 percent, and for more than 10 g. a day it was 9.5 percent.

Smitt (*20*) found a prevalence of ulceromembranous gingivitis of 2.5 percent in Dutch Navy recruits. In those who smoke 50 g. of tobacco for a week or more, the prevalence was 10.5 percent.

Frandsen, et al. (*9*) investigated the correlation between the form of tobacco used and occurrence of gingivitis in Danish Marines. He found that 1,848 cigarette smokers and 273 pipe smokers had essentially the same rates of simple marginal and ulceromembranous gingivitis.

Arno, et al. (*1*) and Herulf (*11*) have investigated alveolar bone changes in smokers. Arno studied 728 men between the ages of 21 and 45 and found that alveolar bone loss, measured as the percentage of maximum height adjacent to the mesial and distal surfaces of each tooth present, was higher among those with high tobacco consumption. The author suggested that tobacco consumption is a complicating factor in periodontal disease and when accompanied by poor oral hygiene

and unfavorable systemic background may help speed up the destruction of the supporting tissues of the teeth.

Herulf measured interdental boney septa in 389 men and 215 women at the Institute of Dentistry in Stockholm. He, too, found a significant relationship between smoking and bone loss.

The relationship between cigarette smoking and edentulism has been studied by Summers, et al. (*22*) in a sample of residents of Tecumseh, Mich. Information on 324 dentulous and 84 edentulous people revealed that among males in both groups those with the greatest evidence of periodontal disease smoked significantly more cigarettes than those with medium or little evidence of the disease. Solomon, et al. (*21*) found significantly more edentulism and advanced periodontal disease in both men and women who smoked cigarettes than in nonsmokers of the same age.

Jackson (*12*) has cited heavy smoking as a factor in delayed healing of tooth sockets after extraction.

Stomatitis nicotina is a form of palatal leukoplakia (*4*). It is characterized by raised umbilicated papules with small central red depressions located primarily on the soft palate and the posterior region of the hard palate. The papules represent blocked palatal mucus glands and the red depressions are their inflamed duct orifices. Saunders (*18*) notes that the lesions begin as tiny red dots and may progress very rarely to ulceration. Although it sometimes occurs in cigar and cigarette smokers, stomatitis nicotina is found most frequently in pipe smokers (*4, 5, 19*). According to Chapman, et al. (*4*), pipe smoking points a stream of smoke directly onto the palate, thereby allowing longer contact between it and the smoke than in other forms of tobacco use. The condition disappears with the cessation of smoking (*6, 7, 8, 14, 18, 19, 24*), though Kerr (*13*) warns that healing may be slow, sometimes requiring months before no lesions are present.

Thoma (*23*) observed a patient who wore dentures for over 40 years and showed lesions of stomatitis nicotina only on the part of the palate that was not covered by the prosthesis. He concluded that the changes were due to local surface rather than to systemic influences.

Lewis (*14*), Saunders (*18*), and Thoma, et al. (*24*) advise biopsy to rule out malignancy in advanced cases. Forsey, et al. (*8*) feel that no association between stomatitis nicotina and cancer has been demonstrated.

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