CHAPTER 2

ADVANCES IN KNOWLEDGE OF THE HEALTH CONSEQUENCES OF SMOKING

CONTENTS

INTRODUCTION

The purpose of this Chapter is to summarize and compare the state of biomedical knowledge concerning tobacco and health in 1989 with that presented in the 1964 Surgeon General's Report (see Table 13). The Chapter addresses major tobacco-related disorders that are well documented in the medical literature; it does not consider many areas of current research that may prove to be important but are in an early or provisional state of investigation.

The 1964 Surgeon General's Report was a landmark publication that included a survey of more than 7,000 available scientific articles on smoking and health. The Advisory Committee that prepared the 1964 Report reviewed and assessed epidemiologic, clinical, pathological, and experimental data for evidence linking smoking to disease. To reach conclusions concerning the causality of associations between smoking and disease, the Committee constructed a framework for evaluating the evidence. With regard to causality, the Committee concluded:

> The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability. To judge or evaluate the causal significance of the association between attribute or agent and the disease, or effect upon health, a number of criteria must be utilized, no one of which is an all-sufficient basis for judgment. These criteria include:
>
> a) the consistency of the association
>
> b) the strength of the association
>
> c) the specificity of the association
>
> d) the temporal relationships of the association
>
> e) the coherence of the association (US PHS 1964).

These criteria were applied throughout the 1964 Report. When the word "cause" was used in the 1964 Report, it was felt to convey "the notion of a significant, effectual relationship between an agent and an associated disorder or disease in the host." Use of the word "cause" in relation to cigarette smoking did not exclude other agents as causes; rather, the members of the Advisory Committee shared "a common conception of the multiple etiology of biological processes."

The principal findings on the health effects of smoking were summarized in the Surgeon General's 1964 Report as follows:

1. Cigarette smoking is associated with a 70-percent increase in the age-specific death rates of men.
2. Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction.
3. Cigarette smoking is the most important of the causes of chronic bronchitis in the United States and increases the risk of dying from chronic bronchitis and

emphysema. A relationship exists between cigarette smoking and emphysema, but it has not been established that the relationship is causal.

4. It is established that male cigarette smokers have a higher death rate from coronary artery disease than nonsmoking males. Although the causative role of cigarette smoking in deaths from coronary disease is not proven, the Committee considers it more prudent from the public health viewpoint to assume that the established association has causative meaning than to suspend judgment until no uncertainty remains.
5. Pipe smoking appears to be causally related to lip cancer. Cigarette smoking is a significant factor in the causation of cancer of the larynx in men. The evidence supports the belief that an association exists between tobacco use and cancer of the esophagus, and between cigarette smoking and cancer of the urinary bladder in men, but the data are not adequate to decide whether these relationships are causal.
6. Women who smoke cigarettes during pregnancy tend to have babies of lower birthweight. It is not known whether this decrease in birthweight has any influence on the biological fitness of the newborn.
7. Epidemiologic studies indicate an association between cigarette smoking and peptic ulcer that is greater for gastric than for duodenal ulcer.
8. The habitual use of tobacco is related primarily to psychological and social drives, reinforced and perpetuated by the pharmacologic actions of nicotine.

Since 1967, the U.S. Department of Health and Human Services has transmitted to the U.S. Congress mandated reports on the health consequences of smoking. Some of the reports have been encyclopedic reviews similar to the 1964 Report, whereas others have focused on the relationship between smoking and a specific topic. The Federal unit charged with preparing these annual reports, the Office on Smoking and Health, now has more than 57,000 documents on smoking and health in its Technical Information Center database.

Research performed during the subsequent 25 years has substantiated and strengthened the conclusions of the 1964 Advisory Committee. Studies published since 1964 have also established associations between smoking and disease in areas for which data did not exist in 1964, shed light on pathogenetic mechanisms of tobacco-related disease, and added scientific depth to areas mentioned only briefly in the 1964 Report.

PART I: HEALTH CONSEQUENCES

Smoking and Overall Mortality [See Chapter 3 for more detailed discussion]

The major prospective studies of the disease risks associated with smoking completed in the 1960s and 1970s contributed substantially to an understanding of the relationship between smoking and disease (US DHEW 1979). These studies provided estimates of both the relative and attributable risks related to cigarette and other types of smoking (Table 1) (US DHEW 1979). Male cigarette smokers had approximately 70 percent higher overall death rates than nonsmokers; the excess mortality of female

TABLE 1.--Mortality ratios of current cigarette-only smokers, by cause of death in eight prospective epidemiologic studies

Cause of death	British doctors[1]	Males in 25 States[2]		U.S. veterans[3]	Japanese study[4]	Canadian veterans[5]	Males in 9 States[6]	Swedish[7]		California occupations[8]
		45-64	65-79					Males	Females	
All cancers[a] (140-205)		2.14	1.76	2.21	1.62		1.97			
Cancer of lung and bronchus (162-163)	14.0	7.84	11.59	12.14	3.64	14.2	10.73	7.0	4.5	15.9
Cancer of larynx (161)		6.09	8.99	9.96	13.59		13.10			
Cancer of buccal cavity (140-141)	13.0[b]			4.09	7.04	3.9[b]	2.80			
Cancer of pharynx (145-148)		9.90[c]	2.93[c]	12.54	2.81					1.0
Cancer of esophagus (150)	4.7	4.17	1.74	6.17	2.57	3.3	6.60			
Cancer of bladder and other (181)	2.1	2.20	2.96	2.15	0.98	1.3	2.40	1.8	1.6	0.7
Cancer of pancreas (157)	1.6	2.69	2.17	1.84	1.83	2.1		3.1	2.5	6.0
Cancer of kidney (180)		1.42	1.57	1.45	1.11	1.4	1.50			
Cancer of stomach (151)		1.42	1.26	1.60	1.51	1.9	2.30	0.9	2.3	
Cancer of intestines (152-153)				1.27	1.27	1.4	0.50			0.8
Cancer of rectum (154)	2.7	1.01[d]	1.17[d]	0.98	0.91	0.6	0.80			0.9
All cardiovascular disease (330-334, 400-468)		1.90	1.31	1.75			1.57			
CHD (420)	1.6	2.08	1.36	1.74	1.96	1.6	1.70	1.7	1.3	2.0
Cerebrovascular lesions (330-334)	1.3	1.38	1.06	1.52	1.14	0.9	1.30	1.0	1.1	1.8
Aortic aneurysm (nonsyphilitic) (451)	6.6	2.62	4.92	5.24		1.8		1.6		
Hypertension (440-447)		1.40	1.42	1.67	2.51	1.6	1.20	1.3	1.4	1.0
General arteriosclerosis (450)	1.4			1.86		3.3	2.00	2.0	2.0	

TABLE 1.--Continued

Cause of death	British doctors[1]	Males in 25 States[2] 45-64	Males in 25 States[2] 65-79	U.S. veterans[3]	Japanese study[4]	Canadian veterans[5]	Males in States[6]	Swedish[7] Males	Swedish[7] Females	California occupations[8]
All respiratory disease (nonneoplastic)							2.85			
Emphysema and/or bronchitis	24.7			10.08			2.30	1.6	2.2[f]	4.3
Emphysema without bronchitis (527.1)		6.55	11.41	14.17		7.7				
Bronchitis (500-502)				4.49		11.3				
Respiratory tuberculosis (001-008)	5.0			2.12	1.27					
Asthma (241)				3.47						
Influenza and pneumonia (480-498)	1.4	1.86	I .72	1.87		1.4	2.60			2.4
Certain other conditions										
Stomach ulcer (540)	2.5[e]	4.06	4.13	4.13	2.06[e]					
Duodenal ulcer (541)		2.86	1.50	2.98		6.9	2.16			0.5
Cirrhosis (581)	3.0	2.06	1.97	3.38	1.35	2.3	1.93	2.4	0.8	4.0
Parkinsonism (350)	0.4			0.26						
All causes	1.64	1.88	1.43	1.84	1.22	1.52	1.70	1.4	1.2	1.78

[a]Numbers in parentheses represent International Classification of Diseases (ICD) codes.
[b]Includes cancers of larynx, buccal cavity, and pharynx.
[c]Includes cancers of buccal cavity and pharynx.
[d]Includes cancers of intestines and rectum.
[e]Includes stomach ulcer and duodenal ulcer.
[f]Includes emphysema, bronchitis, and asthma.
SOURCE: Studies cited are as follows: [1]Doll and Hill (1956); [2]Hammond (1966): [3]Kahn (1966); [4]Hirayama (1967); [5]Best, Josie, Walker (1961); [6]Hammond and Horn (1958);[7]Cederlof et.al (1975);[8]Dunn, Linden, Breslow (1960). US DHEW (1979).

cigarette smokers was somewhat less than that of men, but it increased over the followup intervals. A strong dose-response relationship was found between exposure to cigarette smoke and excess mortality; cessation of cigarette smoking was associated with a decrease in this excess mortality. The relative risks were greater for smoking-related cancers and chronic obstructive pulmonary disease (COPD) than for coronary heart disease (CHD); however, because of the higher mortality rates for CHD the smoking-attributable mortality associated with CHD accounted for over one-third of the excess mortality due to smoking-related diseases.

There have been relatively few long-term longitudinal studies that have measured the overall effects of cigarette smoking since these earlier reports. Results from a new American Cancer Society (ACS) prospective study (Cancer Prevention Study II, CPS-II) and a detailed discussion of total smoking-related mortality are presented in Chapter 3. Based on this study, cigarette smoking is currently estimated to account for 21 percent of all CHD deaths, 30 percent of all cancer deaths, and 82 percent of all COPD deaths.

The Multiple Risk Factor Intervention Trial (MRFIT) is a recent prospective study that screened 361,662 men aged 35 to 57 years between 1972 and 1974 and has been following them since then, both through the Social Security Administration and the National Death Index files. To gauge smoking status, only the number of cigarettes smoked per day at enrollment was reported. Because former smokers were included in the nonsmoker category, the risk comparisons in this study between nonsmokers and smokers are conservative in estimating the effects of smoking. Findings for the 6 years of followup for the MRFIT enrollees screened from 1972-73 are consistent with the studies reported in the 1960s despite changes in the type of cigarettes in terms of tar and nicotine yield and the increased use of filters (see later section of this Chapter and Chapter 5). The MRFIT study shows that smoking status and number of cigarettes smoked per day have remained powerful predictors for total mortality and the development of CHD, stroke, cancer, and COPD. In the study population, there were an estimated 2,249 (29 percent) excess deaths due to smoking, of which 35 percent were from CHD and 21 percent from lung cancer. The nonsmoker-former smoker group had 30 percent fewer total cancers than the smoking group over the 6-year followup.

A study of a random sample of 25,129 Swedish men between 1964 and 1979 evaluated the relationship between cigarette smoking (prevalence of 32 percent), pipe smoking (27 percent), cigar smoking (5 percent), and subsequent mortality (Table 2; Carstensen, Pershagen, Eklund 1987). The all-cause relative death rate was 1.7-fold higher for those smoking greater than 15 g of tobacco per day (estimated as 16 to 25 cigarettes equaling 20 g or a package of pipe tobacco lasting 1 to 4 days equaling 16 g). The relative risks associated with cigarette smoking were consistent both with those of the current MRFIT sample and the earlier cohorts from the 1950s and 1960s. The risks were also increased for pipe and cigar smokers for many of the causes of death.

Epidemiologic studies have shown that cigarette smoking exerts an adverse effect on mortality in older as well as younger age groups. The 17-year followup of the Alameda County Study (Kaplan et al. 1987) demonstrates an increased risk of death even among older cigarette smokers. The adjusted relative risk of death among smokers at entry was 1.46 (age 60 to 69) and 1.43 at age 70 or more. Smoking remained the strongest

predictor of mortality even in this older age group. Other studies have also substantiated that smoking remains an important risk factor in the older age groups (Jajich, Ostfeld, Freeman 1984).

TABLE 2.--Mortality ratios for selected causes in Swedish males, 1964-1979, by type of smoking

Cause of death	Type of smoking [a]		
	Cigarettes only	Pipe only	Cigars only
Cancer of oral cavity and larynx (140-146, 148, 161)[b]	2.9 (8)	1.4 (3)	0.6 (1)
Cancer of esophagus (150)	3.7 (9)	3.6 (6)	6.5 (2)
Cancer of liver and biliary passages (155-156)	3.0 (13)	1.7 (5)	7.2 (4)
Cancer of pancreas (157)	3.3 (28)	2.8 (19)	1.0 (l)
Cancer of trachea, bronchus, and lung (162)	7.4 (77)	7.2 (59)	7.6 (11)
Cancer of bladder (188)	4.2 (17)	4.0 (16)	1.9 (1)
Ischemic heart disease (410-414)	1.48 (399)	1.39 (366)	1.16 (42)
Aortic aneurysm (nonsyphilitic) (441)	2.1 (11)	2.1 (11)	5.1 (4)
Bronchitis and emphysema (490-492)	3.3 (18)	3.6 (16)	1.3 (1)
Peptic ulcer (531-534)	2.0 (11)	2.8 (13)	4.0 (3)
Cirrhosis of liver (571)	1.8 (21)	0.7 (4)	2.7 (3)
Suicide, accidents, and violence (E800-E999)	1.7 (90)	0.9(35)	2.5 (10)
All causes	1.45 (1,063)	1.29 (866)	1.39 (131)

NOTE: Death rates standardized for age and residence. Never smokers constitute the reference group. Number of deaths are given in parentheses.

[a]The mean grams of tobacco smoked per day in 1963, standardized for age and residence, was estimated to be 10.7 in cigarette smokers, 8.4 in pipe smokers, and 13.5 in cigar smokers.

[b]Numhers in parentheses are ICD-8 codes.

SOURCE: Carstensen. Pershagen, Ekhmd (1987).

Lung Cancer

Introduction

One of the most prominent conclusions of the 1964 Report was the determination that "Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect far outweighs all other factors. The data for women, though less extensive, point in the same direction." The epidemiologic evidence available in 1964 on smoking and lung cancer was already extensive. Sharply increasing lung cancer mortality rates in the United States across the 20th century provided indisputable documentation of a new epidemic. Clinical observations and early epidemiologic findings suggested that tobacco smoking was associated with lung cancer, but hypotheses related to air pollution, occupation, and other factors were also extant. By 1964, however, the epidemiologic data, derived from 29 retrospective and 7 prospective studies, were conclusive: smoking was causally related to cancer of the lung. Further support for this conclusion was obtained from animal studies showing that condensates of tobacco smoke were carcinogenic and from the demonstration that tobacco smoke contained carcinogens (US DHHS 1982). The evidence compiled through 1964 also provided additional insight into quantitative aspects of respiratory carcinogenesis by tobacco smoke. The risk of lung cancer was shown to increase with the amount and duration of smoking and to decline with cessation of smoking.

In the 25 years since the 1964 Report, voluminous evidence has continued to support the causal relationship between smoking and lung cancer. The new evidence has been sufficient to establish that smoking also causes lung cancer in women; more comprehensive epidemiologic data have provided expanded descriptions of dose-response relationships between smoking and lung cancer risk. Research has also been directed at environmental and host factors determining susceptibility to tobacco smoke. New investigative techniques in molecular and cellular biology are now providing insight into the molecular mechanisms of carcinogenesis by tobacco smoke.

Dose-Response Relationships

The 1964 Report reviewed evidence from retrospective and prospective epidemiologic investigations that documented dose-response relationships between lung cancer risk and measures of exposure to tobacco smoke. This evidence was cited by the 1964 Report in relation to the criterion of strength of association for determining causality. Investigation of dose-response relationships for lung cancer has subsequently been extended. Mathematical models have been applied to the epidemiologic data to gain biological insight into respiratory carcinogenesis. The cigarette has evolved substantially since 1964 with modifications designed to reduce tar and nicotine yields. Recent research has addressed the risks of smoking the newer products. Studies of lung cancer and involuntary smoking have examined lung cancer risks at low dose levels (US DHHS 1986a).

Abundant epidemiologic evidence has shown dose-response relationships of lung cancer risk with cigarettes smoked per day, degree of inhalation, and age at initiation

of regular smoking. For the purpose of illustration, selected examples of dose-response relationships from two of the early, large prospective epidemiologic studies are reviewed here. Figure 1 shows lung cancer mortality ratios for males by the number of cigarettes smoked per day. For those who smoked more than 40 cigarettes per day, the risk of dying of lung cancer was 23 times greater than the risk experienced by nonsmokers.

Figure 2 illustrates the lung cancer mortality ratios for males by self-reported degree of inhalation of cigarette smoke. These data confirm that even those who reported "just puffing" on cigarettes still had a significantly increased risk of lung cancer. Those who reported inhaling "none" or "slightly" experienced a risk of developing lung cancer that was eight times greater than that of nonsmokers. The relative risk increased to 17 for those who inhaled deeply.

Figure 3 shows lung cancer mortality ratios for males by the age they began smoking. The risk of developing lung cancer was greatest for those who began smoking at an early age.

Mathematical modeling of dose-response relationships, in the biological framework of a multistage model of carcinogenesis, has provided further insight into the nature of dose-response relationships for smoking and lung cancer. Using data from the prospective study of British doctors, Doll and Peto (1978) have performed the most widely cited analysis. They compared regular smokers and lifelong nonsmokers and showed that lung cancer incidence increased with the square of the amount smoked daily, but with the duration of smoking raised to a power of 4 to 5. This finding implies that duration of smoking is the stronger determinant of lung cancer risk and that initiation of smoking during the teenage years will have serious consequences for lung cancer risk (Peto 1986).

Commercial cigarettes have continuously evolved through the addition of filters and other modifications designed to reduce tar and nicotine yields (US DHHS 1981). Since extensive modification of the cigarette began in the 1950s it has only recently become possible to investigate smokers with predominant use of the newer products. Evidence from prospective and case-control studies and assessment of temporal trends of lung cancer mortality indicate somewhat lower risks for cigarettes with reduced tar and nicotine yield, although the risks remain markedly higher than for nonsmokers (US DHHS 1982).

Doll and Peto (1981) examined trends of lung cancer mortality in males in the United States, Britain, and other European countries. They concluded that the international differences and the temporal trends were generally consistent with the tar yields and tar intakes across time and across countries.

Relevant information is also available from case-control and prospective studies. In the United States, investigations spanning the 1960s and 1970s have shown somewhat reduced lung cancer risks in smokers who switched from nonfilter to filter cigarettes (Bross and Gibson 1968; Wynder, Mabuchi, Beattie 1970; Hammond et al. 1976; Wynder and Stellman 1979). More recent studies continue to document lower risks in smokers of filter cigarettes compared with smokers of nonfilter cigarettes. In a case-control study conducted in Western Europe, the relative risk for lifelong nonfilter cigarette smokers was approximately twice that for smokers of filter cigarettes alone

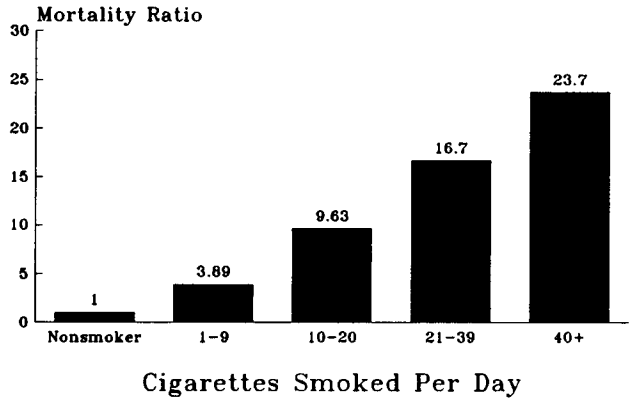

FIGURE 1.—Lung cancer mortality ratio for males by cigarettes smoked per day
SOURCE: U.S. Veterans (Kahn 1966).

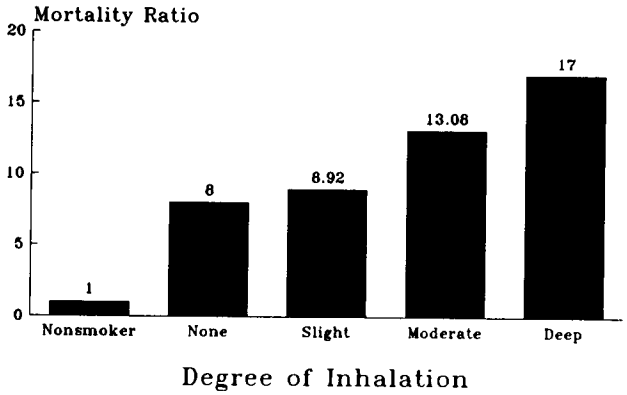

FIGURE 2.—Lung cancer mortality ratio for males by degree of inhalation
SOURCE: CPS-I (Hammond 1966).

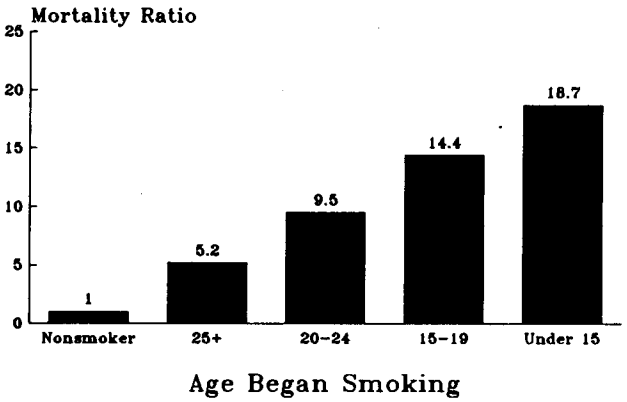

FIGURE 3.—Lung cancer mortality ratio for males by age began smoking
SOURCE: U.S. Veterans (Kahn 1966).

(Lubin et al. 1984a; Lubin et al. 1984b). However, dose-response relationships could not be demonstrated between relative risk and the proportion of years nonfilter brands were smoked or with a cigarette tar index. Among sustained smokers, switching from nonfilter to filter cigarettes was associated with a small reduction in risk (Lubin et al. 1984a). The results from another recent case-control study conducted in Cuba also did not show a convincing association between tar intake and relative risk of lung cancer (Joly, Lubin, Caraballoso 1983). In New Mexico, a case-control study found that lifelong filter cigarette smokers and smokers of both filter and nonfilter cigarettes were at lower risk than lifelong smokers of nonfilter cigarettes only (Pathak et al. 1986). However, there was no evidence of decreasing risk as the extent of filter smoking increased. In addition, few data are available on the reduced risk of smoking low-tar or filter cigarettes for any other smoking-related disease (see Chapter 3).

Women and Lung Cancer

In 1964, at the time of the first Surgeon General's Report, lung cancer was the leading cause of cancer mortality in males, but was only the fifth leading cause of cancer mortality among women. In 1964, the male-female ratio of death rates from lung cancer was 6.7. The 1964 Report did not determine that smoking was causally related to lung cancer in women, although the suggestive nature of the evidence was cited in the Report's conclusion on lung cancer. The consistency of the male-female differences in lung cancer mortality with temporal trends of smoking was noted.

In the 25 years that have elapsed since the 1964 Report, lung cancer mortality has increased dramatically in women. In 1986, lung cancer and breast cancer were the leading causes of cancer death in U.S. women, accounting for approximately equal numbers of cancer deaths (Figure 4); lung cancer deaths are now projected to have surpassed breast cancer deaths (American Cancer Society 1988). Lung cancer mortality for women now equals that observed for men three decades earlier and the male-female ratio of death rates has now fallen to 2.0.

Since the late 1970s the rise in the age-adjusted death rates of lung cancer among men began to level off (Horm and Kessler 1986). In contrast, lung cancer death rates among women continue to climb (Figure 4). As Figures 4 and 5 demonstrate, lung cancer is the only major cancer whose death rates have increased substantially and steadily since the 1930s. The dramatic increase among women began approximately 30 years after the increase for men, consistent with the later adoption of smoking by women; the slope of the curve for women appears to be nearly identical to that of men 30 years earlier. Figure 4 also demonstrates that among women, the lung cancer death rate closely approximated the breast cancer death rate in the mid-1980s. Illustrative of the importance of lung cancer in overall cancer mortality is the fact that, excluding lung cancer, the Nation's age-adjusted cancer death rate fell by 13 percent from 1950 through 1982. Including lung cancer, the rate increased by 8 percent (Bailar and Smith 1986).

The mounting evidence on smoking and lung cancer in women led to a strengthening of the tentative conclusion in the 1964 Report. The 1971 Report concluded that "Cigarette smoking is a cause of lung cancer in women but accounts for a smaller

proportion of cases than in men" (US DHEW 1971). The conclusion of the 1979 Report was similar (US DHEW 1979). The 1980 Report (US DHHS 1980), concerned with smoking and women, and the 1982 Report (US DHHS 1982), concerned with smoking and cancer, comprehensively reviewed the epidemiologic data and reaffirmed the earlier conclusions concerning the causal association of smoking and lung cancer in

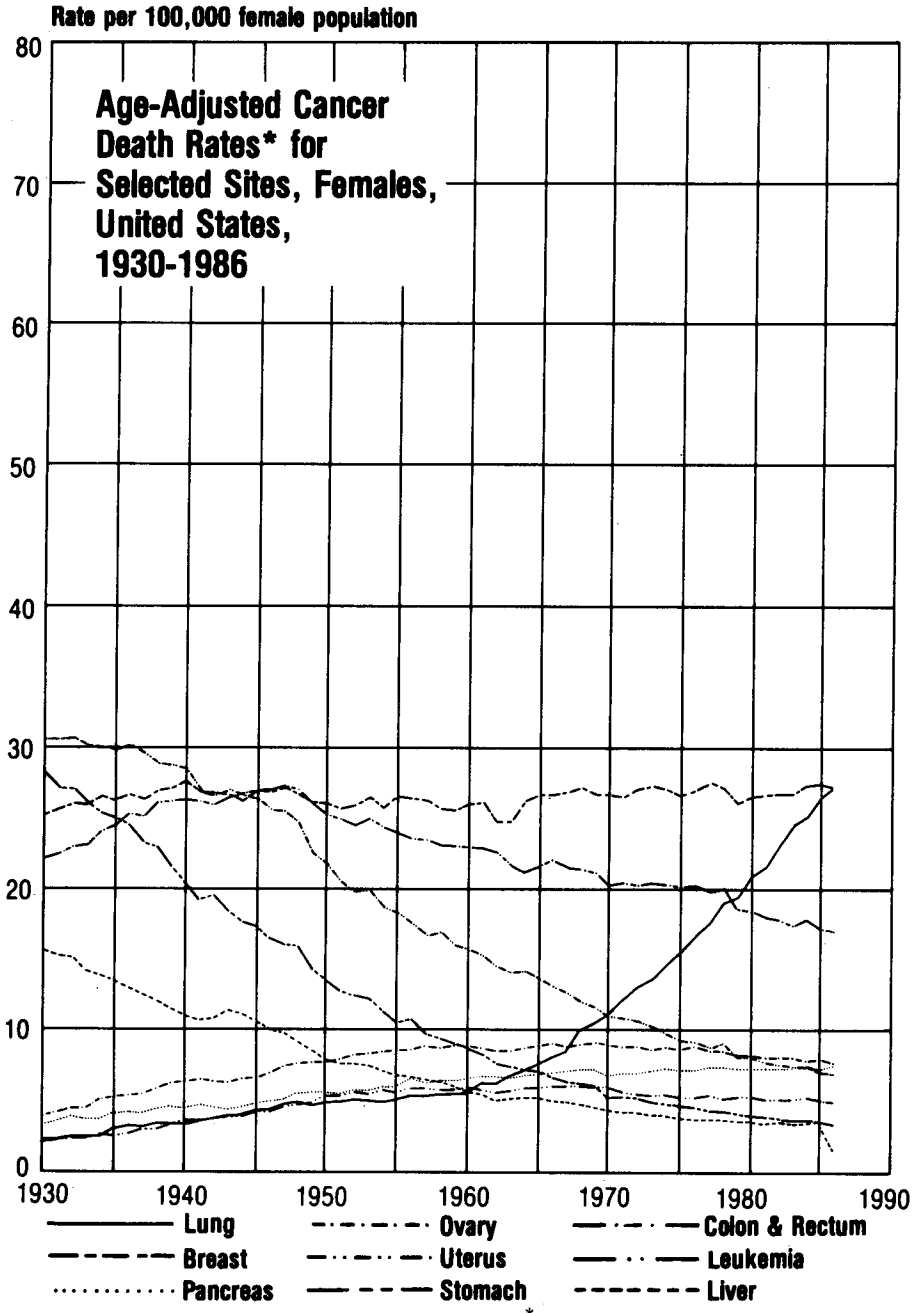

FIGURE 4.—Age-adjusted cancer death rates* for selected sites, females, United States, 1930–86

*Adjusted to the age distribution of the 1970 U.S. Census population.

SOURCES OF DATA: National Center for Health Statistics; U.S. Bureau of the Census.

women; the evidence also provided comprehensive descriptions of dose-response relationships with findings similar to those reported previously for men. Recently reported dose-response relationships from the American Cancer Society Cancer Prevention Study I I for lung cancer and women extend these observations (Figure 6).

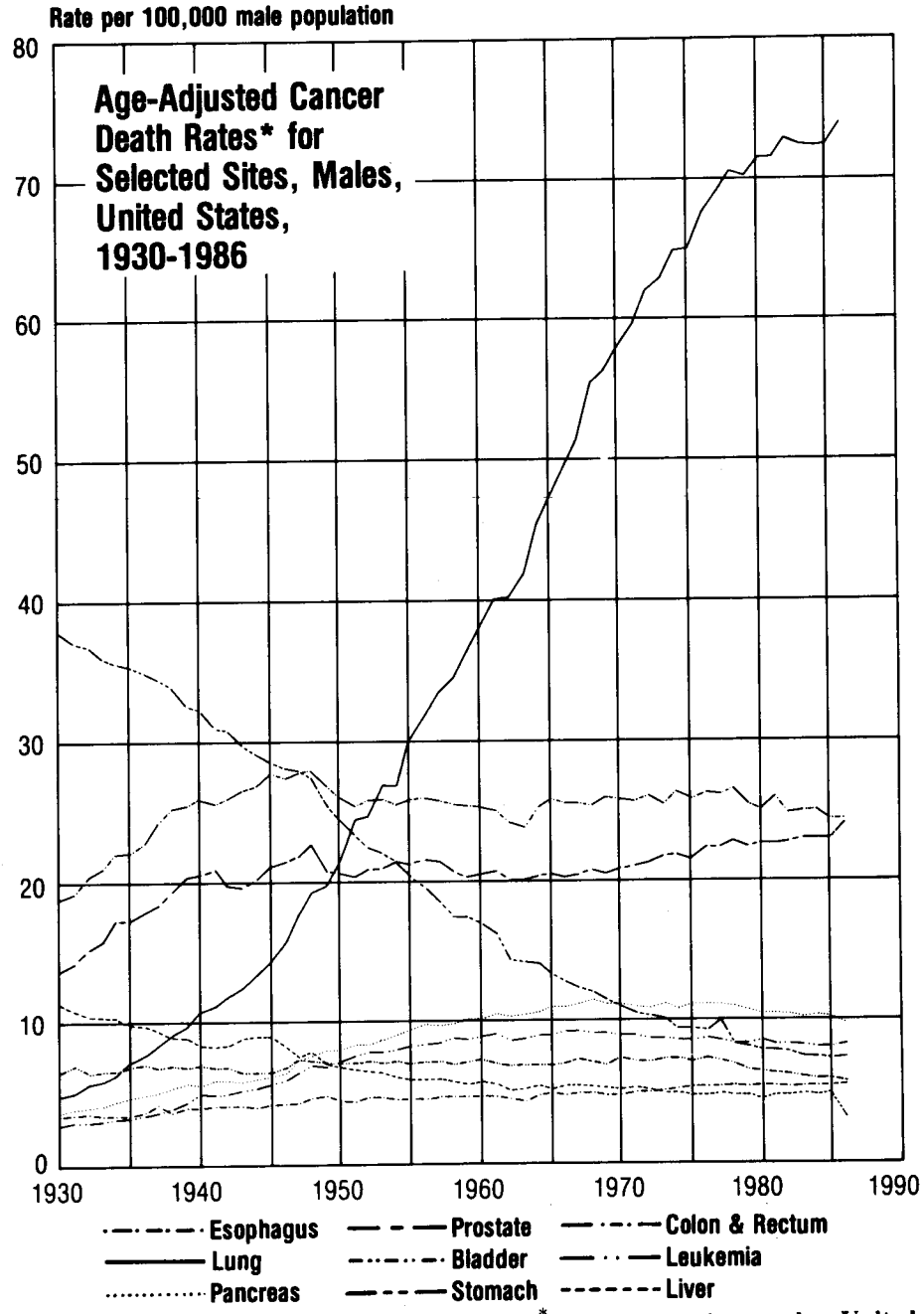

FIGURE 5.—Age-adjusted cancer death rates* for selected sites, males, United States, 1930–86

*Adjusted to the age distribution of the 1970 U.S. Census population.

SOURCES OF DATA: National Center for Health Statistics; U.S. Bureau of the Census.

These data also dramatically illustrate that the current lung cancer epidemic in women is confined to those who smoke cigarettes (Figure 7).

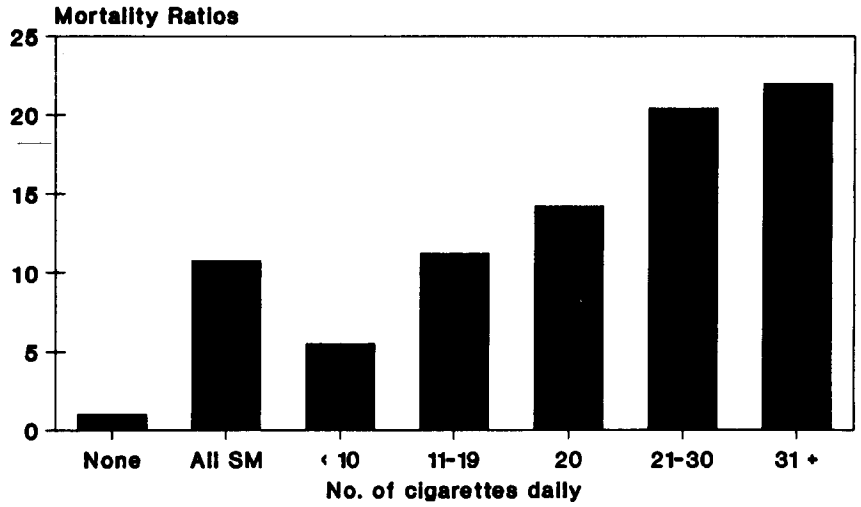

FIGURE 6.—Lung cancer mortality ratios of female cigarette smokers, compared to never smokers, by daily cigarette consumption

SOURCE: CPS-II 1982–86, ACS.

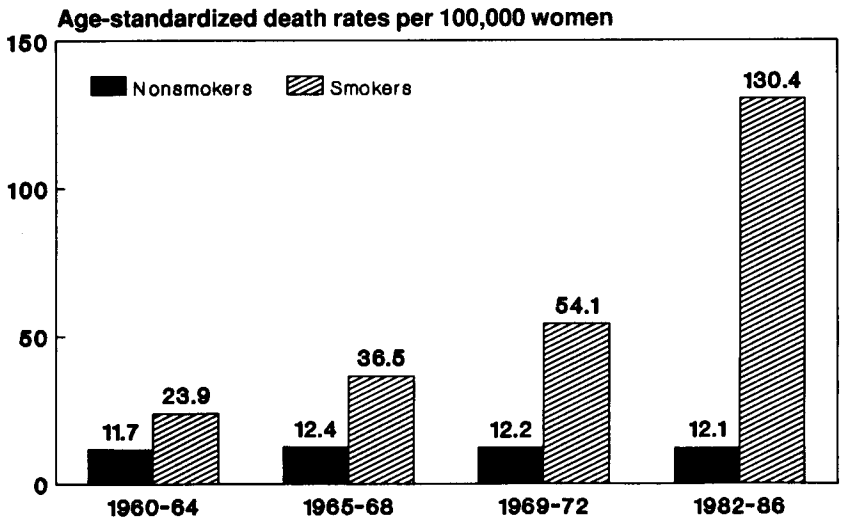

FIGURE 7.—Lung cancer death rates among females over time

SOURCE: CPS-I and CPS-II, ACS.

Type of Lung Cancer and Smoking

At the time of the 1964 Surgeon General's Report, the Kreyberg classification of lung tumors was being investigated. Group 1 Kreyberg tumors included the epidermoid and small-cell histology types; Group 2 Kreyberg tumors included adenocarcinoma and bronchioalveolar cell types. It was felt at that time that the Group 1 tumors, but probably not the Group 2 tumors, were associated with smoking. The 1982 Surgeon General's Report noted that smoking was related to all four major types of lung cancer: epidermoid, small cell, large cell, and adenocarcinoma.

A detailed study of trends in type of lung cancer has been reported from Olmsted County, MN, a region where a large percentage of medical care is provided through the Mayo Clinic. The investigators measured the incidence by type of lung cancer over a 45-year period. The incidence rates for squamous (epidermoid), adenocarcinoma, small-cell, and large-cell lung cancer all increased during this time (Figure 8) (Beard et al. 1985). Adenocarcinomas are more common than other cell types among nonsmokers, in whom lung cancer is rare.

Pipe and Cigar Smoking

Mortality ratios for lung cancer in those who have always smoked only cigars or pipes are significantly higher than in nonsmokers (US DHHS 1982). The mortality ratios are lower, however, than among those who have always smoked cigarettes. The risk of lung cancer increases in relation to the number of cigars smoked per day, the number of pipesful smoked per day, and the degree of smoke inhalation. The lower risk of lung cancer among pipe and cigar smokers compared with cigarette smokers is due to the lesser amount of tobacco smoked and the lower degree of inhalation.

Chemical analysis of the smoke from pipes, cigars, and cigarettes indicates that carcinogens are found in similar levels in the smoke of all these tobacco products. Additionally, experimental studies have shown that in a variety of animal models, smoke condensates from pipes and cigars are equally, if not more, carcinogenic than condensates from cigarettes (US DHEW 1979).

Determinants of Susceptibility

Since the 1964 Report, substantial epidemiologic and experimental investigation has been directed at the determinants of susceptibility to tobacco smoke; both environmental exposures and host characteristics have been investigated. The identification of determinants of susceptibility not only would further understanding of the mechanisms of carcinogenesis by tobacco smoking, but would offer new approaches for prevention of lung cancer by identification of smokers at higher risk. Synergistic interactions among risk factors may place persons with particular combinations of exposures at higher risk for lung cancer.

Interactions among risk factors, such as cigarette smoking and occupational exposures, may be either synergistic or antagonistic; synergism refers to an increased effect of the independent exposures when both are present, whereas antagonism refers to

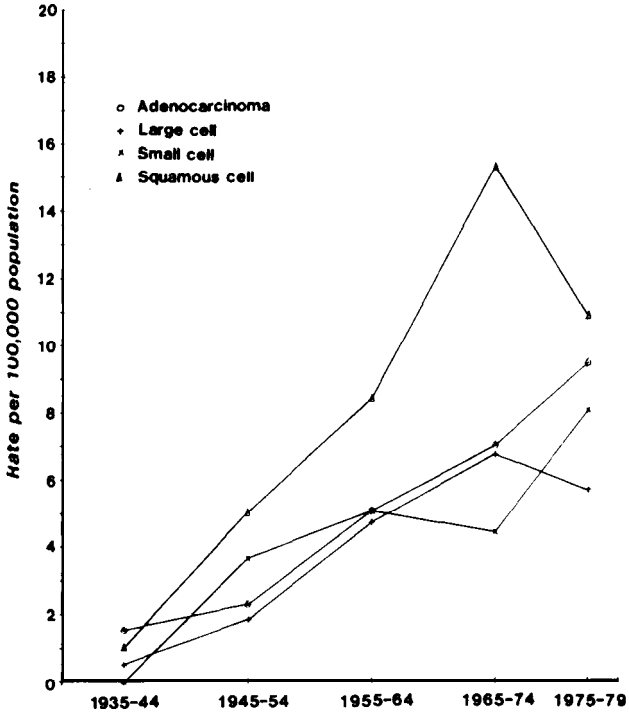

FIGURE 8.--Mean annual incidence rates per 100,000 population for males of bronchogenic carcinoma by cell type, Olmsted County, MN, 1935-79, by decade

SOURCE: Beard et al. (1985).

a reduced effect. Statistical methods are used with epidemiologic data to describe interactions. Either an additive or a multiplicative scale may be used to measure interaction statistically (Saracci 1987). For two exposures, on an additive scale, the sum of the two independent relative risks reduced by one is compared with the relative risk observed when both exposures are present. On a multiplicative scale, the comparison relative risk value is the product of the two independent relative risks. For public health purposes, a positive departure from additivity is considered to represent synergism (Saracci 1987). As the extent of interaction increases, the proportion of the excess cases attributable to the interaction also increases (Saracci 1987).

This Section briefly reviews the current evidence on host characteristics and environmental agents that may modify the risk of cigarette smoking.

Familial Factors

The 1964 Report considered and dismissed the "constitutional hypothesis" that predilections to cigarette smoking and to lung cancer share a common genetic origin. The Report did consider that genetic factors might determine susceptibility for a minority of cases. Subsequent epidemiologic studies have provided empirical evidence of possible genetic or familial determinants of susceptibility (Tokuhata and Lilienfeld 1963a. 1963b; Samet, Humble, Pathak 1986; Ooi et al. 1986). For example, in a recent case-control study in New Mexico (Samet, Humble, Pathak 1986) a parental history of lung cancer was associated with a fivefold increase in lung cancer risk, after adjustment for cigarette smoking. Clinical studies of selected families have also indicated familial aggregation (Brisman et al. 1967; Lynch et al. 1982; Goffman et al. 1982).

Research has not yet identified the mechanisms underlying the familial aggregation of lung cancer. In 1973, Kellermann, Shaw, and Luyten-Kellerman (1973) reported the promising observation that patients with lung cancer had a higher degree of inducibility of aryl hydrocarbon hydroxylase than did control subjects. Because this enzyme converts polycyclic aromatic hydrocarbons to more active carcinogens and because enzyme concentrations are under genetic control, this observation suggested a possible genetic determinant of lung cancer risk. However, not all subsequent studies have been confirmatory, and the inheritance of inducibility in humans has not yet been fully described (Mulvihill and Bale 1984).

Other Host Factors

Acquired host characteristics have also been examined as determinants of lung cancer risk including pulmonary tuberculosis, chronic bronchitis, COPD, disorders associated with interstitial fibrosis of the lung, and peripheral pulmonary scars. However, the evidence related to these disorders is incomplete and frequently is derived from case series rather than from epidemiologic investigations. Recent epidemiologic evidence, however, has indicated increased lung cancer risk for smokers with COPD compared with unaffected smokers (Peto et al. 1983; Samet, Humble, Pathak 1986; Skillrud, Offord, Miller 1986).

Occupational Exposures

Diverse agents inhaled in the workplace have been shown to cause lung cancer. lnteraction between occupational exposures and smoking was the focus of the 1985 Report of the Surgeon General (US DHHS 1985). That Report concluded that "For the majority of American workers who smoke, cigarette smoking represents a greater cause of death and disability than their workplace environment." The Report also highlighted the limitations of the evidence on interactions between smoking and occupational exposures.

Little new information has become available since the 1985 Report. The evidence remains strongest for interactions of smoking with exposure to radon decay products and with exposure to asbestos (Saracci 1987). For both exposures, the preponderance

of the evidence indicates synergism (Doll and Peto 1985; National Research Council 1988), although the results of some individual investigations are inconsistent with synergism.

Ambient Air Pollution

The 1964 Report noted that lung cancer mortality rates tended to be higher in urban than in rural locations. Air pollution was considered a plausible explanation for these differences. The association of lung cancer with atmospheric pollution derives biological plausibility from the presence of carcinogens in polluted air and has some support from epidemiologic data. However, epidemiologic investigation of ambient air pollution as a risk factor for lung cancer has been hampered by methodological problems, including the necessity of considering cigarette smoking and the difficulty of assessing pollution exposure (NIH 1986). Recent epidemiologic investigations have not shown strong effects of air pollution (Samet et al. 1987; Buffler et al. 1988); and Doll and Peto (1981), in their review of the causes of cancer, estimated that only 1 to 2 percent of lung cancer was related to air pollution.

Indoor Air Pollution

As the hazards posed by ambient air pollution from conventional fossil fuels have diminished in some countries, the relevance of indoor air quality for health has become increasingly apparent. Studies of time-activity patterns demonstrate that residents of more developed countries, including the United States, spend on average little time outdoors (Spengler and Sexton 1983; Samet, Marbury, Spengler 1987). Indoor spaces may be polluted by entry of contaminants from outdoor air and by indoor sources including those related to human activity, such as tobacco smoking, building materials, combustion devices, personal care and other household products, and other sources. A trend of reduced building ventilation in the aftermath of the energy problems of the 1970s may have worsened indoor air quality.

Two pollutants in indoor air have been causally linked to lung cancer: environmental tobacco smoke (ETS) (US DHHS 1986a) and radon (National Research Council 1988). The evidence on ETS and cancer was comprehensively reviewed in the 1986 Report (see Section on Involuntary Smoking in this Chapter).

Radon is an inert gas that is formed from radium during the natural decay of uranium. The predominant source of radon in indoor air is the soil beneath structures. Radon diffuses through the ground into basement and crawl spaces, and then throughout the air in a home, or crosses cracks and other penetrations in homes on concrete slabs to enter the indoor environment. Radon daughters are invariably present in indoor air and a wide range of concentrations has been observed in homes (Samet et al. 1988). Some homes have levels comparable to those measured in uranium mines, but the majority of homes probably have levels that are currently considered acceptable.

Radon decays into short-lived particulate decay products. Two of the decay products emit alpha particles, which are highly effective in damaging cells because of their high energy and high mass. When these alpha emissions take place within the lung, the

epithelial lining of the tracheobronchial tree may be damaged and lung cancer may ultimately result. Extensive epidemiologic data from studies of uranium and other underground miners have established a causal association between exposure to radon daughters and lung cancer (National Research Council 1988). The committee on the Biological Effects of Ionizing Radiation (BEIR) IV concluded that the studies of miners indicated synergism between cigarette smoking and radon decay products (National Research Council 1988). The evidence, however, was not considered adequate to determine if the interaction was multiplicative or submultiplicative.

To date, epidemiologic investigations of domestic radon daughters as a risk factor for lung cancer have been limited and preliminary (Samet et al. 1988). However, it is assumed that radon decay products are carcinogenic in the indoor environment as they are in the mining environment. Dosimetric analyses indicate equivalent carcinogenicity in the domestic and mining environments (National Research Council 1988). Thus, radon must be considered one of the most important factors interacting with cigarette smoking. All smokers are exposed to radon, some at unacceptable levels. Quantitative estimates of the contribution of radon to lung cancer are variable. The estimates vary with the underlying assumptions and the risk model employed (Samet et al. 1988).

Although cigarette smoking is by far the major cause of lung cancer, radon must also be considered a cause of the disease. The public health burden of radon-related lung cancer is substantially increased by the synergism between cigarette smoking and radon exposure.

Diet

Diet has recently been considered as potentially influencing the risk of lung cancer in smokers. Nutrients of particular interest include preformed vitamin A, carotene, vitamin E, and vitamin C (Colditz, Stampfer, Willett 1987).

An enlarging body of experimental and epidemiologic evidence supports the hypothesis that the risk for certain cancers varies inversely with consumption of preformed vitamin A or beta-carotene, its precursor (Peto et al. 1981; National Academy of Sciences 1982; Colditz, Stampfer, Willett 1987). The biological plausibility of this hypothesis derives from the known effects of vitamin A deficiency on the differentiation of epithelial surfaces, from in vitro and in vivo models, which show that retinoids can suppress the development of malignancy, and from possible anticarcinogenic activity of beta-carotene, the principal dietary precursor of vitamin A (Peto et al. 1981; National Academy of Sciences 1982). The epidemiologic evidence indicates a protective effect of dietary vitamin A intake from vegetable sources, but not of preformed vitamin A, which is derived from meat and dairy sources, and vitamin supplements. Clinical trials on vitamin A and lung cancer risk are in progress.

Vitamins E and C are antioxidants, which might have anticancer effects. To date, the epidemiologic data on these vitamins are sparse and inconclusive (Colditz, Stampfer, Willett 1987).

Smoking Cessation

Cessation of cigarette smoking results in a gradual decrease in lung cancer risk. Several of the prospective and retrospective epidemiologic studies have demonstrated a reduction in lung cancer risk over time following smoking cessation. One example is provided from the U.S. Veterans study (Kahn 1966) (Figure 9).

Other recent studies have continued to confirm the benefit of smoking cessation for lung cancer risk (Lubin et al. 1984b; Alderson, Lee, Wang 1985; Pathak et al. 1986; Higgins, Mahan, Wynder 1988). For example, Lubin and colleagues (1984b) described the pattern of reduction in risk following smoking cessation in a case-control study that involved 7,181 lung cancer patients and 11,006 controls. For men and women in this study who had smoked for less than 20 years and had not smoked for 10 years, the risks of lung cancer were approximately the same as those of lifelong nonsmokers. On the basis of the study of British physicians, Peto and Doll (1984) have suggested that the effect of cigarette smoking cessation is to fix the age-specific risk of lung cancer at the rate achieved at the time of cessation, based on the smoking history up to that time. According to this analysis, the former smoker's relative risk of lung cancer declines as the background rate for lung cancer rises with age.

Therefore, smoking cessation is clearly beneficial in reducing the risk of lung cancer compared with continued smoking; but cessation may not reduce the risk to the levels of a lifetime nonsmoker even after many years of cessation. (See Table 2, Chapter 3.)

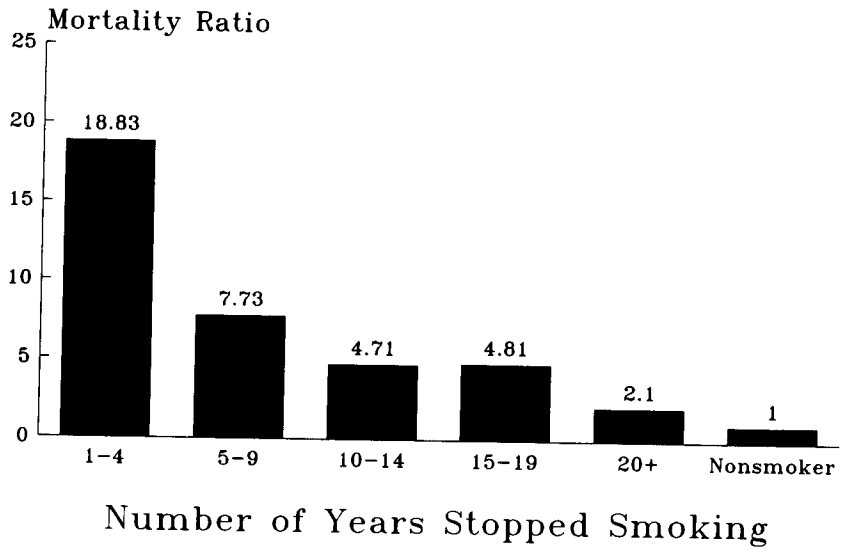

FIGURE 9.—Lung cancer mortality ratio for male former smokers
SOURCE: U.S. Veterans (Kahn 1966).

Laryngeal, Oral, and Esophageal Cancer

The 1964 Surgeon General's Report concluded that cigarette smoking was causally related to laryngeal cancer in men and that pipe smoking was causally related to lip cancer (US PHS 1964). Subsequent reports reviewed the accumulating epidemiologic evidence that established that cancers of the larynx, oral cavity, and esophagus are caused by smoking in both men and women. The mortality ratios for these cancers are similar for smokers whether they smoke cigars, pipes, or cigarettes. A strong dose-response relationship exists, and the risk decreases with cessation, compared with continued smoking. Recent studies have confirmed these findings (Blot et al. 1988; Elwood et al. 1984; Schottenfeld 1984). (See Chapter 3.)

Alcohol consumption is also a risk factor for oral, pharyngeal, laryngeal, and esophageal cancer. The combination of alcohol and smoking produces a synergistic increase in risk. In one study (Schottenfeld 1984), for all upper airway cancers combined, the risk was 8.6 for those smoking 30 or more cigarettes per day in combination with 20 oz of alcohol consumed per week.

Bladder and Kidney Cancer

A relationship between smoking and bladder cancer was noted in the 1964 Surgeon General's Report. The 1979 Report concluded that cigarette smoking acts independently and probably acts synergistically with other risk factors to increase the risk of bladder cancer. The 1982 Surgeon General's Report concluded that cigarette smoking is a contributory factor for both bladder and kidney cancer. Cigarette smoking is estimated to account for 30 to 40 percent of bladder cancer (US DHHS 1982).

Recent studies have confirmed earlier findings. For bladder cancer, in both men and women, cigarette smokers have a relative risk of 2 to 3. A dose-response relationship has been demonstrated, and the risk of bladder cancer decreases following smoking cessation (McLaughlin et al. 1984; Hartge et al. 1987; Zahm, Hartge, Hoover 1987).

There is a positive association between smoking and kidney cancer, with relative risks ranging from 1 to more than 5. The increased risk of kidney cancer due to cigarette smoking is found for both males and females, and there is a dose-response relationship, as measured by the number of cigarettes smoked per day.

Pancreatic Cancer

The first Surgeon General's Report did not examine the relationship between smoking and cancer of the pancreas. Several subsequent reports of the Surgeon General have noted that cigarette smoking is a contributory factor for pancreatic cancer.

The major prospective epidemiologic studies have consistently shown an increased risk of pancreatic cancer among both male and female cigarette smokers. The mortality ratio for cigarette smokers compared with nonsmokers is generally in the range of 2 to

3. A detailed review of the epidemiology of pancreatic cancer was written by Gordis and Gold (1984).

For those in the MRFIT Study who smoked 40 or more cigarettes a day, the mortality ratio for pancreatic cancer was 2.3 compared with nonsmokers. Other recent studies (Mack et al. 1986; Whittemore et al. 1985) report that cigarette smoking is strongly and consistently related to pancreatic cancer. Most epidemiologic studies show a dose-response relationship between cigarette smoking and pancreatic cancer for both men and women and a gradual decline in the risk of developing pancreatic cancer following smoking cessation (US DHHS 1982; Mack et al. 1986).

Autopsy studies report hyperplastic changes in the pancreatic duct cells and atypical changes in their nuclei among cigarette smokers compared with nonsmokers. The pancreas is probably exposed to tobacco carcinogens or carcinogenic metabolites present in bile or blood (US DHHS 1982).

Stomach Cancer

The 1964 Surgeon General's Report reviewed smoking and stomach cancer and, on the basis of the limited evidence available at that time, concluded that there was no relationship between smoking and stomach cancer. Evidence from prospective and retrospective studies available more recently has shown a small but consistent increase in mortality ratios, averaging approximately 1.5 for smokers compared with nonsmokers. Dose-response relationships have been demonstrated for the number of cigarettes smoked per day. The 1982 Surgeon General's Report concluded that cancer of the stomach is associated with cigarette smoking.

Cervical Cancer

Cancer of the uterine cervix was not reviewed in the 1964 Surgeon General's Report. The 1982 Report of the Surgeon General reviewed the studies published up to that time and concluded that further research was necessary to define whether there was an association between cigarette smoking and cervical cancer.

There are several risk factors for cervical cancer including early and frequent coitus, multiple sexual partners, pregnancy at an early age, and the presence of sexually transmitted diseases. Some of these risk factors may also be associated with smoking.

Winkelstein and coworkers (1984) reviewed 12 studies dealing with smoking and cervical cancer, and in most studies there was a positive relationship that could not be explained by other risk factors. Two studies published in 1985 confirmed these findings (Clarke et al. 1985; Greenberg et al. 1985).

Baron and coworkers (1986) reported on a case-control study of 1, 174 patients with cervical cancer. Cigarette smoking was associated with a statistically significant increase in risk for cervical cancer. LaVecchia and associates (1986) in Italy studied the relationship between cigarette smoking and the risk of cervical neoplasia in a case-control study of 183 women with intraepithelial neoplasia. Cigarette smoking was associated with an increased risk of intraepithelial neoplasia and invasive cancer. This association could not be totally explained by potential confounding factors. In a case-

control study of 480 patients with cervical cancer, there was a 50-percent excess risk of cancer among cigarette smokers (Brinton et al. 1986). This excess risk persisted after adjustment for sexual practices associated with smoking such as age at first intercourse and number of sexual partners. There was a twofold excess risk of cervical cancer for women who smoked more than 40 cigarettes per day. The dose-response relationship persisted after adjusting for several variables. There was no increased risk of cervical cancer among former smokers.

The finding of nicotine and cotinine in the cervical secretions of cigarette smokers (Sasson et al. 1985) and of mutagenic mucus in the cervix of smokers (Holly et al. 1986) complements the epidemiologic findings.

In summary, more than 15 epidemiologic studies have consistently shown an increased risk for cervical carcinoma in cigarette smokers compared with nonsmokers. Supportive clinical studies provide a plausible biological basis for the relationship. The available data confirm an association between cigarette smoking and carcinoma of the uterine cervix.

Endometrial Cancer

Several studies have reported that endometrial cancer is less frequent among women who smoke cigarettes than among nonsmokers (Baron et al. 1986). Cigarette smoking exerts an antiestrogenic effect that may explain this inverse association. The public health significance of this association is limited because of the overall adverse impact of cigarette smoking on morbidity and mortality.

Coronary Heart Disease

The 1964 Surgeon General's Report (US PHS 1964) noted that male cigarette smokers have higher death rates from CHD than nonsmokers. Subsequent reports concluded that cigarette smoking can cause death from CHD and that smoking is one of the major independent risk factors for heart attack, manifested as fatal and nonfatal myocardial infarction and sudden cardiac death. Smoking also increases the risk of heart attack recurrence among survivors of a myocardial infarction (US DHEW 1979). The 1980 Report (US DHHS 1980) noted the increased risk of CHD among women who smoke. It also described the synergistic interaction between smoking and oral contraceptive use that substantially increases CHD risk. The 1983 Report (US DHHS 1983) stated that cigarette smoking is a major cause of CHD and noted the decreased risk of CHD among former smokers compared with current smokers.

Epidemiology

The findings from several prospective studies involving more than 20 million person-years of observation in North America, Northern Europe, and Japan have been remarkably similar: cigarette smokers are at increased risk for fatal and nonfatal myocardial infarction and for sudden death. Overall, smokers have a 70 percent greater

CHD death rate, a two- to fourfold greater incidence of CHD, and a two- to fourfold greater risk for sudden death than nonsmokers (US DHHS 1983).

Although women experience lower CHD rates than men, cigarette smoking is a major determinant of CHD in women. In a recent prospective study of 119,404 female nurses, smoking accounted for approximately one-half of the coronary events (Willett et al. 1987). Cigarette smoking produces a greater relative CHD risk in men and women under 50 years of age than in those over 50 years of age (Glover, Kuber et al. 1982; Rosenberg, Miller et al. 1983).

Dose-response relationships between cigarette smoking and CHD mortality have been demonstrated for several measures of exposure to cigarettes, including the number of cigarettes smoked per day, the depth of inhalation, the age at which smoking began, and the number of years of smoking (US DHHS 1983). Smoking cigarettes with reduced yields of tar and nicotine has not been found to reduce CHD risk (Kaufman et al. 1983).

Coronary Heart Disease Risk Factors

The risk of experiencing a heart attack is multifactorial (US DHHS 1983). The presence of one or more of the major CHD risk factors, cigarette smoking, hypercholesterolemia, and hypertension, identifies individuals at high or very high risk. These risk factors interact synergistically to greatly increase CHD risk (Figure 10). The risk of CHD associated with cigarette smoking is comparable to that associated with the other major CHD risk factors.

The risk of CHD is greatly increased among diabetic men and women who smoke cigarettes (Suarez and Barrett-Connor 1984; Stamler, Wentworth, Neaton 1986), and the sex differences in CHD are substantially reduced among diabetics. Among the MRFIT screenees free of a history of heart attack, there were 5,245 diabetics and 350,977 nondiabetic men aged 35 to 57 years at the time of enrollment (Suarez and Barrett-Connor 1984). The CHD death rate was much higher among diabetics than among nondiabetics. Smokers had higher CHD death rates than nonsmokers among both diabetics and nondiabetics. Six-year CHD mortality was 4.0/1,000 for nonsmokers who were nondiabetic and 23.2/1,000 for diabetics who smoked at least 36 cigarettes per day.

Hyperlipoproteinemia is a primary cause of premature coronary atherosclerosis and heart attacks. Cigarette smoking substantially increases the risk of CHD among individuals with genetic familial hyperlipidemias. Williams and coworkers (Williams et al. 1986; Hopkins, Williams, Hunt 1984) studied four large Utah pedigrees with familial hypercholesterolemia. They noted a substantially increased risk of CHD within the high-risk pedigrees in relation to cigarette smoking.

Miettinen and Gylling (1988) have recently completed a long-term followup of 96 patients with familial hypercholesterolemia. Cigarette smoking was a significant predictor of coronary mortality after adjustment for disease history, sex, and various metabolic parameters.

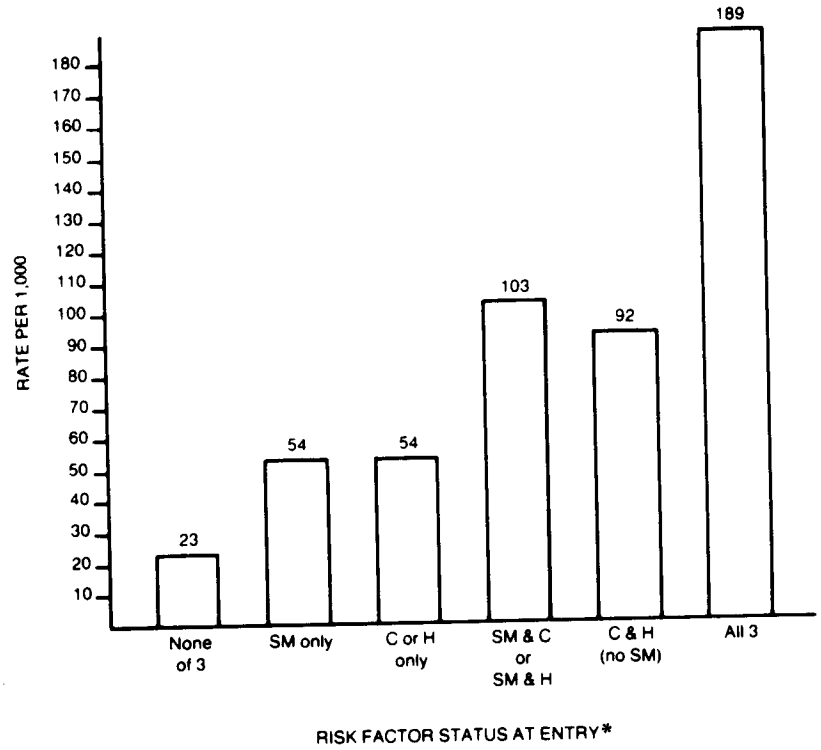

FIGURE 10.—Major risk factor combinations, 10-year incidence of first major coronary events, males aged 30 to 59 years at entry, Pooling Project

*Definitions of the three major risk factors and their symbols: hypercholesterolemia (C), ≥250 mg/dh; elevated blood pressure (H), diastolic pressure ≥90 mm Hg; cigarette smoking (SM), any current use of cigarettes at entry.

NOTE: All rates were age-adjusted by 10-year age groups to the U.S. white male population, 1980.

SOURCE: Pooling Project Research Group (1978).

Pathophysiological Mechanisms

Autopsy studies indicate that cigarette smoking has a significant positive association with atherosclerosis (US DHHS 1983). Studies have noted the strongest relationship of cigarette smoking with aortic atherosclerosis, but smokers also show increased coronary atherosclerosis compared with nonsmokers (US DHHS 1983). Smokers undergoing coronary angiography have more coronary artery disease than nonsmokers (Pearson 1984). Cigarette smokers who continue to smoke following transluminal coronary angioplasty may be more likely to require repeat angioplasty than nonsmokers (Galan et al. 1988)

Cigarette smoking exerts both acute chronic adverse coronary effects (US DHHS 1983; Holbrook et al. 1984). It contributes to acute ischemic and occlusive events through several possible mechanisms: an imbalance between myocardial oxygen supply and demand, coronary artery spasm, a hypercoagulable state, increased platelet adhesiveness and aggregation, and a decreased ventricular fibrillation threshold (US

DHHS 1983; Martin et al. 1984; Fitzgerald, Oates, Nowak 1988). Cigarette smoking also contributes to the development of coronary atherosclerosis. Possible mechanisms for this chronic effect include: repetitive endothelial injury, a decreased high-density lipoprotein (HDL)/low-density lipoprotein (LDL) cholesterol ratio, abnormalities in the synthesis of thromboxane A2 and prostacyclin, and increased neutrophil elastase activity (Holbrook, in press; Nowak et al. 1987: Weitz et al. 1987).

Clinical Correlations

Cigarette smoking has an adverse effect on individuals with symptomatic or asymptomatic CHD. Compared with nonsmokers, smokers having a positive exercise test (Rautaharju et al. 1986; Gordon et al. 1986) or a history of coronary bypass surgery (Vlietstra et al.l986;Kemp et al. 1986) face a worse prognosis. Smokers who have angina pectoris have a higher risk of death than nonsmokers (Hubert, Holford, Kannel 1982) and have a poorer long-term prognosis after a myocardial infarction (Ronnevik, Gundersen, Abrahamsen 1985; Kuller et al. 1982). Continuing to smoke increases the likelihood of recurrent acute myocardial infarction and sudden death (Hallstrom, Cobb, Ray 1986). Smoking may also cause silent ischemic disturbances in patients with stable angina pectoris (Deanfield et al. 1986).

Cigarette smoking interferes with the efficacy of medication used to treat CHD such as propranolol, atenolol, and nifedipine (Deanfield et al. 1984).

Smoking Cessation

Prospective epidemiologic studies have documented a substantial reduction in CHD death rates following smoking cessation (US DHHS 1983). While some studies have shown a benefit within 2 years after quitting, other studies have suggested that the former smoker's CHD risk gradually decreases over a period of several years (Cook et al. 1986). For heavier smokers, the residual CHD risk is proportional to the total lifetime exposure to cigarettes.

Cerebrovascular Disease (Stroke)

In the United States stroke is the third leading cause of death. It is also a major cause of morbidity, with more than 400,000 Americans suffering nonfatal strokes each year (Harrison's Principles of Internal Medicine 1987).

There are two major types of cerebrovascular disease: (1) cerebral infarction due to occlusion of a vessel by an embolus or thrombosis, and (2) cerebral hemorrhage, including subarachnoid and parenchymal. The terms cerebrovascular accident and stroke are nonspecific and usually refer to clinical syndromes.

A stroke may be caused by disease of the extra- or intracranial blood vessels. Embolization from the heart or extracranial arteries is also an important cause of stroke. The stroke can result from hemorrhage from a blood vessel or from occlusion of an artery because of atherosclerosis, thrombosis, or embolization. In the Framingham study, atherothrombotic brain infarction accounted for the majority of strokes (Wolf,

Dawber et al. 1978). Improved diagnostic methods have provided a better categorization of the causes of stroke. Epidemiologic studies have shown that hypertension is the most important risk factor for stroke (US DHHS 1983).

The 1964 Report of the Surgeon General stated that the large epidemiologic studies of Hammond and Horn (1958) and Dorn (1958) had found a moderate increase in the mortality rate from cerebrovascular disease in cigarette smokers compared with nonsmokers.

The 1971 Report (US DHEW 1971) reviewed six major prospective epidemiologic studies. Cigarette smokers in these studies experienced increased stroke mortality compared with nonsmokers. The 1980 Report (US DHHS 1980) noted that women who smoke have an increased risk of subarachnoid hemorrhage. The 1983 Report (US DHHS 1983) reviewed the data associating cigarette smoking with stroke and found an increased risk for stroke among smokers that was most evident in younger age groups. It also noted that women cigarette smokers experience an increased risk for subarachnoid hemorrhage and that the concurrent use of both cigarettes and oral contraceptives greatly increased this risk.

Since the release of the 1983 Surgeon General's Report the relationship between cigarette smoking and stroke has been clarified in several large studies involving men and women.

The risk of stroke was evaluated in a prospective study of 8,006 Japanese-American men living in Hawaii (Abbott et al. 1986). After 12 years of followup, cigarette smokers had two to three times the risk of thromboembolic or hemorrhagic stroke compared with nonsmokers. The increased risk was independent of other risk factors such as hypertension and CHD. Those smokers who stopped smoking during the course of the study experienced more than a 50-percent reduction in the risk of stroke compared with continuing smokers.

The impact of cigarette smoking on stroke incidence was assessed prospectively in the Framingham Study of 4,255 men and women (Wolf et al. 1988). This cohort was followed for 26 years, and the diagnoses were confirmed by clinical examination. Cigarette smoking made a significant, independent contribution to the risk of stroke. The risk increased as the number of cigarettes smoked increased. Smoking cessation resulted in a significant decrease in stroke risk so that 5 years after stopping smoking the risk was at the level of nonsmokers.

The relationship between cigarette smoking and the risk of stroke was evaluated in a prospective study of 118,539 middle-aged women who were followed for 8 years (Colditz, Bonita, Stampfer 1988). Compared with nonsmoking women, those who smoked 1 to 14 cigarettes per day had a relative risk of fatal and nonfatal stroke of 2.2. Those who smoked 25 or more cigarettes per day had a relative risk of fatal and nonfatal stroke of 3.7. In this latter group of women, the relative risk of subarachnoid hemorrhage was 9.8. The contribution of cigarette smoking to increased stroke risk was independent of other risk factors. Smoking cessation resulted in a prompt decrease in stroke risk; the relative risk of stroke in women who had stopped smoking for 2 years was 1.4, compared with women who had never smoked. The authors of this study also reviewed eight prospective cohort studies and seven case-control studies involving

women, and concluded that most of these studies had shown a positive association between cigarette smoking and stroke (Table 3).

In the ongoing study of approximately 1.2 million persons (CPS-II), cigarette smokers under the age of 65 years experienced increased risks of death from stroke. For men and women (current smokers), the relative risks of death from stroke were 3.7 and 4.9, respectively. The relative risks for those over age 65 years were 1.9 and 1.5 for men and women, respectively (Chapter 3).

Cigarette smoking was associated with decreased cerebral blood flow in a recent clinical study involving 192 normal volunteers (Rogers, Meyer et al. 1983). In a subsequent study of 268 normal volunteers, abstention from cigarette smoking improved cerebral perfusion (Rogers, Meyer et al. 1985).

As already noted in this Chapter, cigarette smoking increases the risk for CHD, and consequently for congestive heart failure, both of which increase the risk for stroke. Data from the Medical Research Council study on the treatment of mild hypertension illustrate the impact of cigarette smoking on the efficacy of drug therapy and stroke incidence (Medical Research Council Working Party 1985). Nonsmokers receiving propranolol to control hypertension experienced a reduction in stroke incidence, while cigarette smokers did not.

Wolf and coworkers (1988) recently reviewed the association between cigarette smoking and stroke and concluded that it is causal. These investigators noted that the causal connection is supported by all of the traditional epidemiologic criteria; these include an increased risk for stroke among smokers compared with nonsmokers that is independent of other risk factors, a dose-response relationship, and a decrease in stroke risk with smoking cessation (Abbott et al. 1986; Wolf et al. 1988; Colditz, Bonita, Stampfer 1988). The aforementioned recent clinical studies also confirm that cigarette smoking increases the risk for stroke. Thus, current evidence indicates that cigarette smoking is a cause of stroke and that smoking cessation reduces the risk for stroke.

Atherosclerotic Peripheral Vascular Disease

Lower extremity arterial vascular disease causes substantial mortality and morbidity; the complications may include intermittent claudication, tissue ischemia and gangrene, and ultimately, loss of the limb.

The 1964 Surgeon General's Report commented that little is known about the relationship of smoking to peripheral arteriosclerosis. Subsequent reports have described the evidence establishing that cigarette smoking is a cause of and the most powerful risk factor for atherosclerotic peripheral vascular disease and that smoking cessation is the most important intervention in the management of this problem (US DHEW 1971, 1979; US DHHS 1983).

Cigarette smoking is directly related to the extent of atherosclerotic disease involving large and small arteries in the lower extremity (Criqui et al. 1985). Cigarette smoking also causes peripheral vasoconstriction. Epidemiologic and clinical studies have clearly demonstrated that cigarette smokers have a higher prevalence than nonsmokers

TABLE 3.—Summary of studies of cigarette smoking and stroke in women

First author	Cohort size	Type of stroke	No. of cases	Relative risk	Comments
		Prospective cohort studies			
Colditz	118,539	All	274	2.2 (95% CI, 1.5–3.3) 2.7 (95% CI, 1.9–3.7) 3.7 (95% CI, 2.7–5.1)	1–14 cigarettes/day 15–24 cigarettes/day ≥25 cigarettes/day
Salonen	4,334	Infarction Other	21 38	1.4 (90% CI, 0.4–5.0) 0.8 (90% CI, 0.3–2.2)	
Tanaka	1,681	Hemorrhage Infarction	30 81	2.1 (NS) 1.0 (NS)	Included 780 men
Sacco	2,421	Subarachnoid hemorrhage	22	1.6	Relative risk was 2.9 for heavy smokers
Vessey	17,000	Subarachnoid hemorrhage Nonhemorrhagic	13 33	3.0 1.4	
Doll	6,194	Cerebral thrombosis	68	0.5 for 15–24 cigarettes/day	Risk tended to decrease with amount smoked
Layde	46,000	Subarachnoid hemorrhage	20		Smokers had higher risk of fatal subarachnoid hemorrhage
Petitti	16,759	Subarachnoid hemorrhage Other	11 23	5.7 (90% CI, 1.8–17.8) 4.8 (90% CI, 2.3–9.8)	
Wolf	2,421	All	238	1.6 ($p<0.025$)	
		Case–control studies			
Taha		Subarachnoid hemorrhage	124	2.6 for aneurysm	Based on 68 female cases
Bell		Subarachnoid hemorrhage	134	3.7(90% CI, 2.3–5.9)	
Collaborative study		Hemorrhage Thrombosis	192 140		Smoking doubled risk No increased risk
Abu-Zeid		Hemorrhage Thrombosis	137 410	1.4 (NS) 2.4 ($p<0.001$)	Included men
Bonita		Subarachnoid hemorrhage	70	4.7 (95% CI, 2.9–7.6)	Dose–response relationship not significant
Bonita		Not subarachnoid hemorrhage	53	2.6 (95% CI, 1.4–4.6)	
Herman		Stroke	125	1.2 (95% CI, 0.7–2.3)	Included 78 men

NOTE: CI, confidence interval; NS, not significant.

SOURCE: Colditz, Bonita, Stampfer (1988).

of both symptomatic and asymptomatic lower extremity arterial disease (US DHHS 1983).

In the Lipid Research Clinic prevalence study (Pomrehn et al. 1986), 48 percent of individuals with claudication were current cigarette smokers compared with 30 percent of the controls. Smoking was twice as frequent among individuals developing leg pain, compared with those not developing leg pain, during the exercise test. In the Framingham Study, the risk of developing intermittent claudication was directly and strongly related to cigarette smoking (Kannel and Shurtleff 1973).

Diabetes mellitus and cigarette smoking are the key risk factors for lower extremity arterial disease and subsequent amputation. Peripheral neuropathy and lower extremity arterial disease and infection predispose individuals with diabetes to gangrene and amputation (Herman, Teutsch, Geiss 1987). Diabetics have a sixteenfold increased risk of lower extremity amputation compared with nondiabetics; about 50 percent of the lower extremity amputations in the United States are performed on diabetics. Approximately 31,000 American diabetics undergo such surgery each year. The disease tends to be more progressive and occurs at younger ages in diabetic smokers than in nonsmokers.

In a study in Sweden, practically all diabetic patients under the age of 60 years with gangrene were cigarette smokers (Lithner 1983). The prevalence of lower extremity arterial disease was evaluated for diabetic subjects. One-third of the smokers had evidence of peripheral vascular disease compared with only 16 percent of the nonsmokers. Diabetics who stopped smoking for at least 2 years had a 30 percent lower prevalence of lower extremity arterial disease than those who continued to smoke.

Epidemiologic studies in a Rochester, MN, population (Zimmerman et al. 1981) demonstrated that for 1,073 residents over the age of 30 who were diagnosed with diabetes mellitus between 1945 and 1969, about 8 percent of men and 7 percent of women had clinical evidence of peripheral vascular disease at the time that diabetes was diagnosed. The annual incidence of lower extremity arterial disease among the diabetics was 21/l,000 for men and 17.6/l,000 for women; about 20 percent had gangrene and 36 percent had intermittent claudication. Among diabetics with lower extremity arterial disease, 77 percent of men and 43 percent of women had been cigarette smokers compared with 55 percent of normal control men and 36 percent of normal control women.

Effective treatment of diabetes mellitus and smoking cessation are the two most important interventions to prevent the development of atherosclerotic peripheral vascular disease.

Atherosclerotic Aortic Aneurysm

The 1964 Report of the Surgeon General commented on the increased mortality rates for aortic aneurysm in cigarette smokers compared with nonsmokers. The 1969 Report concluded that there is a close association between cigarette smoking and death caused by aortic aneurysm. The 1983 Report summarized the epidemiologic data and noted that the mortality rate for abdominal aortic aneurysm was 2 to 8 times greater in cigarette smokers than in nonsmokers. As already noted, pathology studies have shown a sig-

nificant association between cigarette smoking and atherosclerosis that is most striking in the aorta (US DHHS 1983).

Chronic Obstructive Pulmonary Disease

In the 1950s increasing morbidity and mortality from chronic respiratory conditions prompted clinical and epidemiologic investigations of the etiology of chronic bronchitis, emphysema, and related disorders. A variety of terms have subsequently been applied to permanent airflow obstruction in cigarette smokers. In the 1984 Surgeon General's Report, chronic obstructive lung disease (COLD) referred to chronic mucus hypersecretion, airways abnormalities, and emphysema. In this Report, the term COPD is used for the permanent airflow obstruction that develops in cigarette smokers. Thirty years ago, the most widely advanced hypothesis on the etiology of COPD linked progressive lung damage to recurrent respiratory infection and atmospheric pollution (Stuart-Harris 1954). However, epidemiologic investigations, largely carried out in the United Kingdom, quickly indicated the predominant role of cigarette smoking in causing COPD (Stuart-Harris 1968a,b).

By 1964, the evidence was sufficiently compelling to support the conclusion by the Advisory Committee to the Surgeon General that "Cigarette smoking is the most important of the causes of chronic bronchitis in the United States, and increases the risk of dying from chronic bronchitis and emphysema" (US PHS 1964). The Report stopped short of classifying the relationship between cigarette smoking and emphysema as causal, however. The Report also noted the increased prevalence of respiratory symptoms and the reduction of lung function in smokers. The epidemiologic data cited in support of these conclusions were drawn from seven prospective studies of mortality in relation to cigarette smoking and about a dozen surveys of respiratory morbidity; only one prospective study on lung function had been reported at that time.

In the 25 years that have elapsed since the release of the 1964 Surgeon General's Report, the findings of numerous laboratory, clinical, and epidemiologic studies have continued to reaffirm the predominant role of cigarette smoking in causing COPD and have extended understanding of the pathogenesis, pathophysiology, and natural history of this disorder. As the evidence has accumulated, the conclusions of the Surgeon General's Reports on cigarette smoking and COPD have been strengthened. The 1967 Surgeon General's Report labeled cigarette smoking as the most important of the causes of COPD (US PHS 1968). In the 1971 and 1979 Reports, the conclusions of the 1964 and 1967 Reports were strengthened (US DHEW 1979). Increased morbidity and mortality from chronic bronchitis and emphysema were documented in cigarette smokers compared with nonsmokers. Additionally, autopsy evidence confirmed that the lungs of smokers were widely damaged, and the evolving protease-antiprotease hypothesis provided a framework for understanding mechanisms through which cigarette smoke causes emphysema.

The 1984 Surgeon General's Report focused on COLD (US DHHS 1984). The overall conclusion of the Report was: "Cigarette smoking is the major cause of chronic obstructive lung disease in the United States for both men and women. The contribution of cigarette smoking to chronic obstructive lung disease morbidity and mortality

far outweighs all other factors." In contrast to the sparse evidence in the 1964 Report, the 1984 Report reviewed numerous cross-sectional and longitudinal studies of morbidity and mortality. The longitudinal studies described the evolution of the cigarette-related decline in lung function that leads to impairment sufficient to result in a clinical diagnosis of COPD.

This Section provides an overview of the evidence on COPD that has accumulated since the 1964 Report in the areas of pathogenesis, pathophysiology, and natural history of COPD and the role of cigarette smoking.

Pathogenesis

The 1964 Report described the deposition of cigarette-smoke particles and gases in the lungs and the effects of cigarette smoke on lung defenses but did not address the mechanisms by which cigarette smoking causes COPD (US PHS 1964). Much of the subsequent investigation of the mechanism of lung injury by cigarette smoke was sparked by the observation that homozygous deficiency of alpha1-antitrypsin, the major protease inhibitor, is associated with familial panlobular emphysema (Laurell and Eriksson 1963; Eriksson 1964). This observation led to the hypothesis, generally referred to as the protease-antiprotease hypothesis, that the development of emphysema results from an imbalance between proteolytic enzymes and their inhibitors (Janoff 1985; Niewoehner 1988). Cigarette smoking is postulated to produce unchecked proteolytic activity by increasing proteolytic enzyme activity in the lung while decreasing antiprotease activity.

Experimental and clinical observations have been consistent with the protease-antiprotease hypothesis (US DHHS 1984). Observations that smokers, compared with nonsmokers, have an increased number of neutrophils in peripheral blood (Yeung and dy Buncio 1984), in bronchoalveolar lavage fluid, and in lung biopsy specimens (Hunninghake and Crystal 1983) provide indirect evidence for an increased elastase burden in smokers' lungs, since neutrophils are the primary source of elastase (Janoff 1985). Furthermore, elastase levels are elevated in bronchial lavage fluid immediately after smoking cigarettes (Fera et al. 1986). Cigarette smoking has also been shown to decrease the levels and activity of antiproteases, an effect attributed to oxidants in cigarette smoke and the pulmonary macrophages of smokers (Janoff 1985; US DHHS 1984). Animal models confirm that unchecked proteolytic activity can cause emphysema (US DHHS 1984).

The lungs of patients with COPD generally display both emphysema and abnormalities of the small airways. Mechanisms by which cigarette smoke damages small airways have not been so extensively investigated as the factors determining the development of emphysema.

Pathophysiology

The lungs of smokers with COPD generally have both thickening and narrowing of airways and emphysema, although the extent of these two processes is variable (US DHHS 1984). Both the airways changes and emphysema produce airflow obstruction.

The 1964 Report noted that smokers' lungs displayed airways changes and emphysema; however, the pathophysiological correlates of these changes were not explored.

Subsequent investigations, correlating structural changes with function, have described the relationship between smoking-caused changes in lung structure and airflow obstruction. Emphysema and small-airway injury contribute to the physiological impairment found in COPD; in individuals with symptomatic airflow obstruction, either type of injury may be predominant, but both are probably important (US DHHS 1984). While the 1964 Report described effects of cigarette smoking on the airways, the importance of the small airways as a site of airflow obstruction was not recognized until the late 1960s (Hogg. Macklem, Thurlbeck 1968). More recent investigations have confirmed that measures of small-airway injury are correlated with the degree of airflow obstruction (US DHHS 1984; Hale et al. 1984; Nagai, West, Thurlbeck 1985). Autopsy studies have shown that changes in the small airways develop in the lungs of young smokers and antedate the development of symptomatic airflow obstruction (Niewoehner, Kleinerman, Rice 1974).

The importance of emphysema in producing chronic airflow obstruction has also been amply documented since the 1964 Report. Emphysema reduces the driving pressure for expiratory flow and contributes to increased airways resistance by reducing tethering of small airways. In patients with symptomatic airflow obstruction, the extent of anatomic emphysema is correlated with the severity of airflow obstruction, as are small-airway abnormalities (US DHHS 1984; Hale et al. 1984; Nagai, West, Thurlbeck 1985). Thus, the smoking-caused lung changes in the airways and parenchyma have both been unequivocally linked to airflow obstruction.

Natural History of COPD and the Role of Cigarette Smoking

Nearly all the epidemiologic evidence reviewed in the 1964 Report was cross-sectional in nature. These data established that cigarette smoking increased respiratory symptoms and reduced the level of ventilatory function. but they did not provide insight into the temporal evolution of COPD. Subsequent cross-sectional studies have provided more complete quantitative descriptions of the effects of cigarette smoking on lung function, and new longitudinal studies have partially described the evolution of lung function changes in smokers and the factors determining the rate of change over time.

The numerous cross-sectional studies published since the 1964 Surgeon General's Report have shown that cigarette smoking is a strong determinant of the level of ventilatory function, which is most often assessed by the measurement of the 1-sec forced expiratory volume (FEV1). The level of FEVl declines as the amount of smoking increases (US DHHS 1984). Multiple regression techniques have been applied to data from several different populations to describe the quantitative relationship between the amount smoked and loss of ventilatory function. These analyses indicate that ventilatory function declines in a linear fashion with cumulative consumption of cigarettes, usually expressed as pack-years (Burrows et al. 1977; Dockery et al. 1988). For example, based on analysis of data from 8,191 men and women from six U.S. cities, Dockery and others (1988) reported that male smokers of average height lose 7.4 mL of FEV

on average for each pack-year and that women lose 4.4 mL per pack-year. Although the decline in mean level of FEV_1 appears small, the distributions of lung function level in smokers and in nonsmokers are different; the distribution for smokers is skewed toward lower levels so that a much greater proportion of smokers than nonsmokers have levels below the usual limit of normal (Figure 11) (US DHHS 1984; Burrows et al. 1977; Dockery et al. 1988).

The longitudinal studies published since the 1964 Report have partially described the natural history of lung function changes in COPD (Fletcher et al. 1976; US DHHS 1984). Ventilatory function, as measured by FEV_1, for example, increases during

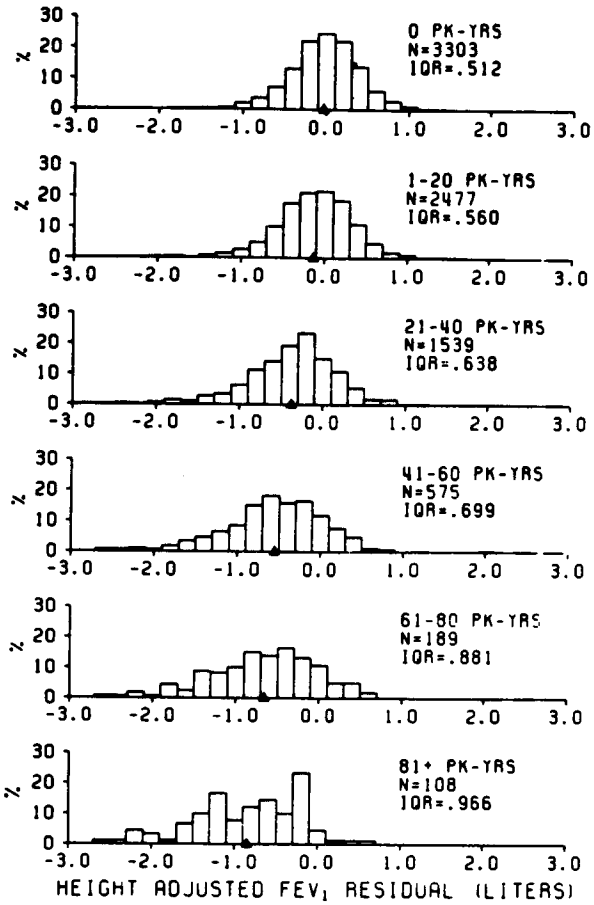

FIGURE 11.—Percent distribution of predicted values of forced expiratory volume in 1-sec (FEV_1) in subjects with varying pack-years of smoking.

NOTE: Triangle indicates mean. IQR is interquartile range.

SOURCE: Dockery et al. (1988).

childhood and reaches a peak level during early adulthood (Figure 12). From the peak level, ventilatory function declines with increasing age. In cigarette smokers who develop symptomatic airflow obstruction, a similar loss of function takes place, but at a more rapid rate than in nonsmokers and in smokers who do not develop disease. A physician is likely to diagnose COPD when continued excessive loss of ventilatory function results in sufficient impairment to cause dyspnea and limitation of activity.

The factors influencing rate of lung function decline in cigarette smokers have not yet been fully characterized. The rate of decline tends to increase with the amount smoked, and former smokers generally revert to the rate of loss of nonsmokers. In fact, the excessive decline observed in some smokers may represent a common physiological consequence of different pathophysiological mechanisms. Habib and coworkers (1987) carefully characterized 13 subjects from a longitudinal study in Tucson with a mean annual decline in FEV_1 greater than 60 mL per year. Clinically, these subjects were not unique and none had $alpha_1$-antitrypsin deficiency. Physiological assessment

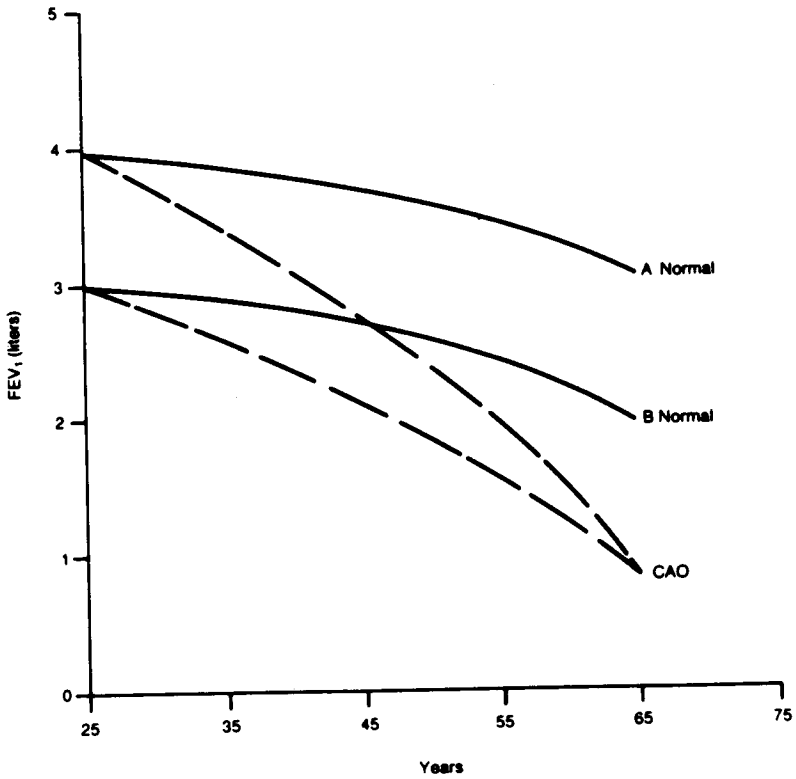

FIGURE 12.—Decline of FEV_1 at normal rate (solid line) and at an accelerated rate (dashed line)

NOTE: A, person who has attained a "normal" maximal FEV_1 during lung growth and development; B, person whose maximal FEV_1 has been reduced by childhood respiratory infection. CAO, chronic airflow obstruction.

SOURCE: Samet et al. (1983).

suggested that some were developing emphysema, whereas others appeared to have disease of the large and/or small airways.

The studies of longitudinal change in lung function have spanned only segments of the full natural history of COPD, and many questions remain unanswered. It is unclear, for example, whether the excessive decline takes place at a constant rate in continuous smokers, as suggested by much of the epidemiologic evidence, or whether the excessive decline occurs intermittently after some triggering event. The factors determining the susceptibility of individuals to cigarette smoking are also unclear. Current hypotheses emphasize determinants of protease-antiprotease imbalance, level of nonspecific airways reactivity, and severe respiratory illness during early childhood.

Since the release of the 1964 Surgeon General's Report, abundant evidence has indicated the overwhelming importance of cigarette smoking in causing COPD; in fact, COPD would be an uncommon condition in the United States without cigarette smoking. Unfortunately, death rates due to COPD have paralleled those for lung cancer and have increased progressively over the last 25 years (National Center for Health Statistics 1986). The trends are consistent with cohort changes in smoking; in this regard, while age-specific rates for males have been increasing at older ages, a recent decline in COPD mortality has been observed at younger ages (US DHHS 1984). While important scientific questions remain unanswered concerning the pathogenesis of COPD, the available evidence provides sufficient rationale for preventing COPD through smoking prevention and cessation.

Pregnancy and Infant Health

Several endpoints have been studied to evaluate the adverse effects of smoking on pregnancy, including (1) infant birthweight; (2) fetal and infant mortality; (3) congenital malformations; (4) fertility; and (5) long-term effects on the child.

The 1964 Report indicated an association between smoking and low-birthweight babies (US PHS 1964), but it did not consider the evidence sufficient to establish a causal relationship.

The 1969 Report (US PHS 1969) confirmed the association between maternal smoking and low-birthweight babies, an increased incidence of prematurity, spontaneous abortions, stillbirths, and neonatal deaths. The 1971 Report (US DHEW 1971) concluded that maternal smoking during pregnancy exerts a retarding influence on fetal growth. The 1973 Report (US DHEW 1973) noted that cigarette smoking is a probable cause of increased late fetal mortality and infant mortality. The 1977-78 Report (US DHEW 1978) noted a dose-response relationship between smoking and abruptio placentae, placenta previa, bleeding during pregnancy, and prolonged premature rupture of membranes, as well as the association of smoking during pregnancy with impaired physical and intellectual development of the offspring. The 1979 Report (US DHEW 1979) linked smoking with sudden infant death syndrome. The 1980 Report (US DHHS 1980) noted that up to 14 percent of preterm deliveries in the United States may be attributed to maternal smoking. It also surveyed studies of men and women suggesting that cigarette smoking may impair fertility.

In 1985, the Center for Health Promotion and Education of the Centers for Disease Control, Atlanta, GA, defined the fetal tobacco syndrome as follows. (1) The mother smoked 5 or more cigarettes a day throughout the pregnancy. (2) The mother had no evidence of hypertension during pregnancy, specifically no preeclampsia and documentation of normal blood pressure at least once after the first trimester. (3) The newborn has symmetrical growth retardation at term, 37 weeks, defined as birthweight less than 2,500 g, and a ponderal index (weight in grams divided by length) greater than 2.32. (4) There is no obvious cause of intrauterine growth retardation, that is, congenital malformation or infection (Nieburg et al. 1985).

Infant Birthweight

A clear dose-response relationship exists between the number of cigarettes smoked during pregnancy and the birthweight deficit (US DHHS 1980; Committee to Study the Prevention of Low Birthweight 1985). Compared with nonsmokers, light and heavy smokers have a 54- and 130-percent increase, respectively, in the prevalence of newborns weighing less than 2,500 g. A review of five studies including 113,000 births in the United States, Canada, and Wales found that from 21 to 39 percent of the incidence of low birthweight was attributed to maternal cigarette smoking (Committee to Study the Prevention of Low Birthweight 1985). Also, cigarette smoking seems to be a more significant determinant of birthweight than the mother's prepregnancy height, weight, parity, payment status, or history of previous pregnancy outcome, or the infant's sex. The reduction in birthweight associated with maternal tobacco use seems to be a direct effect of smoking on fetal growth.

Mothers who smoke also have increased rates of premature delivery. The newborns are also smaller at every gestational age. The infants display symmetrical fetal growth retardation with deficits in measurements of crown-heel length, chest and head circumferences, and birthweight.

A recent study in Boston (Liebetman et al. 1985) attempted to evaluate the reasons for differences in rates of prematurity between blacks and whites. Of the 1,365 black women, 34.7 percent were cigarette smokers compared with only 23.4 percent of the white women. Cigarette smoking and low hematocrit levels were two of the most important risk factors accounting for the differences in prematurity rates between blacks and whites.

Finally, a number of careful studies have found that the effect of cigarette smoking on birthweight is not mediated through decreased maternal appetite or weight gain (US DHHS 1980).

The most widely accepted hypothesis relating maternal smoking and the effects on the fetus and newborn is intrauterine hypoxia (Rush and Cassano 1983). The hypoxia could occur as a result of factors associated with smoking, such as increased levels of carbon monoxide (CO) in the blood, reduction of blood flow, or inhibition of respiratory enzymes. There is strong experimental evidence that maternal smoking causes fetal hypoxia.

Several studies have demonstrated that smoking cessation prior to or during pregnancy can partly reverse the reduction in the child's birthweight (Rush and Cassano 1983; Hebel, Fox, Sexton 1988). In a large study using the 1970 British Birth Cohort (Lieberman et al. 1987) an inverse relationship between measures of social class and the prevalence of smoking was demonstrated that was similar to that seen in the United States. In all social class groups, babies of the nonsmokers weighed more than those whose mothers had smoked during pregnancy, and the women who had stopped smoking either before or during pregnancy had babies with higher birthweights than women who continued to smoke throughout pregnancy.

Fetal and Perinatal Mortality

Kleinman and colleagues (1988) from the National Center for Health Statistics used Missouri birth records from 1979-83 (Table 4) to study the relationship between cigarette smoking in mothers and infant mortality. Among the 134,429 primiparas, the infant mortality rates (adjusted for age, parity, education, and marital status) were (per 1,000 subjects) 15.1 for white nonsmokers, 18.8 for whites who smoked less than 1 pack of cigarettes per day, and 23.3 for whites who smoked more than 1 pack of cigarettes per day. For black nonsmoking women, the infant mortality rate (per 1,000 women) was 26.0; for blacks who smoked less than I pack per day, 32.4; and for blacks who smoked greater than 1 pack per day, 39.9. Mortality was increased during the fetal, neonatal, and postneonatal periods. It was estimated that if all pregnant women stopped smoking, the number of fetal and infant deaths would be reduced by approximately 10 percent. In the United States this would result in about 4,000 fewer infant deaths each year. A study conducted by the Office on Smoking and Health attributed approximately 2,500 infant deaths to maternal smoking in 1984 (CDC 1987).

Stein and associates (1981) have studied the causes of spontaneous abortion in three New York City hospitals. They compared women with spontaneous abortion to controls (women who carried their pregnancy to 28 weeks or more). Within the spontaneous abortion groups, they then compared those with evidence of chromosomal abnormalities and those with apparently normal chromosomes. The odds of a spontaneous abortion increased by 46 percent for the first 10 cigarettes smoked per day and by 61 percent for the first 20 cigarettes smoked. Smoking was not associated with the spontaneous abortion of chromosomally abnormal conceptions, but only with those in which the chromosomes were normal. These results were not confounded by such factors as maternal age or race.

Congenital Malformations

Evidence that exposure to tobacco and cigarette smoking could be related to congenital malformations is less clear. About 3 percent of all live births have major congenital malformations (Behrman and Vaughn 1987). Maternal smoking has not been demonstrated to be a major risk factor for the induction of congenital malformations, although elevated risks have been reported in some studies. Kelsey and coworkers (1978) reported an increased risk of 1.6 for congenital malformations among the

TABLE 4.-Infant mortality rates and odds ratios (95% confidence intervals), by maternal race, among 134,429 primiparas, based on multiple logistic regression, Missouri, 1979-83

	Crude rates (per 1,000)		Adjusted rates (per 1,000)		Adjusted odds ratios	
	Whites	Blacks	Whites	Blacks	Whites	Blacks
Marital status						
Married	14.5	25.4	15.9	29.5	1.00	1.00
Unmarried	24.0	28.6	21.0	27.2	1.33(1.18-1.50)	0.92 (0.73-1.16)
Education (years)						
<12	22.9	33.2	19.8	34.1	1.36(1.16-1.59)	
12	15.2	25.9	16.7	28.8	1.14 (1.02-1.28)	
>12	12.8	21.5	14.6	25.3	1.00	
Age (years)						
<18	24.0	33.7	18.8	32.2	1.24 (1.06-1.45)	
18-19	18.2	26.0	16.3	27.9	1.08 (0.95-1.22)	
20-24	14.2	23.4	15.2	26.0	1.00	
25-29	13.2	27.1	16.1	27.6	1.06 (0.94-1.20)	
30-34	16.1	19.9	18.6	31.9	1.23(1.01-1.50)	
	25.4	69.3	31.1	52.9	2.09 (1.49-2.93)	
Smoking						
0	13.9	25.3	15.1	26.0	1.00	
<1 pack/day	19.1	33.1	18.8	32.4	1.25(1.13-1.39)	
≥1 pack/day	24.3	41.5	23.3	39.9	1.56 (1.37-1.77)	

SOURCE: Kleinman et al. (1988).

offspring of women smoking more than 1 pack of cigarettes per day compared with women reporting no smoking during pregnancy. Similarly, Himmelberger, Brown, and Cohen (1978) reported a 2.3-fold higher risk of congenital abnormalities for smoking mothers than for nonsmokers.

One study has also reported an increased frequency of congenital malformations based on the smoking habits of the father (Schardein 1985). The trends with paternal smoking were independent of maternal smoking level, maternal and paternal age, and social class.

The relatively low incidence of congenital malformations, the different types of malformations, and the various possible biological mechanisms have made the study of the relationship between environmental factors and congenital malformations extremely difficult. New techniques to monitor pregnancy outcomes may enhance our understanding of the interrelationship between cigarette smoking, other environmental factors, and congenital malformations.

Fertility

A recent study has substantiated previous reports that suggested that women who smoke may have reduced fertility (Baird and Wilcox 1985). Data on smoking history and number of noncontraceptive cycles until conception were collected from 678 pregnant women. Of nonsmokers, 38 percent conceived in their first cycle compared with 28 percent of smokers. Smokers were 3.4 times more likely than nonsmokers to have taken greater than 1 year to conceive. After adjustment for other risk factors, it was estimated that the fertility of smokers was 72 percent of that of nonsmokers. Heavy smokers experienced lower fertility than light smokers. Fertility was not affected by the husbands' smoking.

The effects of cigarette smoking on sperm quality in men (Ablin 1986) were also evaluated in relation to density, motility, and morphological abnormalities in 238 age-related smokers and 135 nonsmokers. Spermatozoa from smokers possessed significantly decreased density and motility compared with those from nonsmokers. Morphological abnormalities of the sperm were also noted more frequently among smokers than among nonsmokers (Ablin 1986).

Long-Term Effects on the Child

Relatively few studies have evaluated the long-term consequences of smoking during pregnancy on the child. One of the larger recent studies looked at neurological handicaps among children up to 14 years of age whose mothers had smoked during pregnancy and among control children born in northern Finland in 1966 (Rantakallio and Koiranen 1987). Seventy-eight children of smokers and 62 controls had mental retardation (IQs less than 85), cerebral palsy, or epilepsy. The incidence of mental retardation alone was 15.9/1,000 among the children of the mothers who smoked and 13.9 among the controls. For any combination of mental retardation, cerebral palsy, and epilepsy, the rates were 42.8/1,000 for children of smoking mothers and 34/1,000 for the controls, a relative risk of 1.27 with confidence limits of 0.90 to 1.79.

Naeye and Peters (1984) investigated the mental development of smokers' children by comparing siblings whose mothers smoked in one but not in subsequent pregnancies and found that hyperactivity, short attention span, and lower scores on spelling and reading tests were more frequent for the children whose mother had smoked during pregnancy, but the differences were relatively small, the test scores being only 2 to 4 percent lower. Dunn also studied neurological and electroencephalographic abnormalities among 6-year-old children of smokers and found these conditions to be slightly more common in the children of mothers who had smoked during pregnancy, but again the differences were not statistically significant. Small sample sizes in many of these studies and the relative infrequency of the events of interest limit interpretation of the studies (Dunn et al. 1977).

Peptic Ulcer

The 1964 Surgeon General's Report noted an association between peptic ulcer and cigarette smoking. The 1979 Report stated that the relationship between cigarette smoking and peptic ulcer is significant enough to suggest a causal relationship. Peptic ulcer disease is more likely to occur, less likely to heal, and more likely to cause death in smokers than in nonsmokers.

Cigarette smoking retards the healing of peptic ulcer (Sontag et al. 1984; Lane and Lee 1988; Korman et al. 1983). A large trial of cimetidine, a drug used in the treatment of peptic ulcer, was reported in 1984 by Sontag and associates. Ulcer recurrence was much more frequent among smokers compared with nonsmokers for both the placebo- and the cimetidine-treated groups.

Nicotine decreases pyloric sphincter pressure and therefore permits increased reflux of duodenal contents into the stomach. Nicotine also decreases pancreatic bicarbonate secretion. This may impair neutralization of gastric acid in the duodenum, contributing to the formation and persistence of duodenal ulcers. Smoking cessation probably reduces the incidence of peptic ulcer and is an important component of peptic ulcer treatment even with the available effective drug therapy.

Osteoporosis

The 1964 Report did not discuss osteoporosis. The interest in osteoporosis is fairly recent because of the increasing number of older individuals, especially women, at risk of fracture; the better methods of measuring bone mineral mass; and the understanding of osteoporosis pathophysiology and risk factors.

Osteoporosis leading to fractures, especially of the hip, wrist, and spine, is an important cause of disability and death, predominantly among postmenopausal women. About 15 to 20 million persons in the United States have osteoporosis. Each year about 1.3 million fractures are attributed to this disease (Journal of the American Medical Association 1984).

Smoking may be a risk factor for osteoporosis (Willett et al. 1983). Women smokers have an earlier age of menopause, an important risk factor for osteoporosis (Willett et al. 1983). Smokers may have a lower intake of calcium during adolescence and young

adult life when maximum bone mineral mass is reached (Sandler et al. 1985). Smokers also weigh less than nonsmokers (US DHHS 1988). Obesity substantially reduces the risk of hip fracture (Kiel et al. 1987). Overweight women have higher endogenous estrogen levels and greater bone mass (Cauley et al. 1986). Exogenous estrogen intake among postmenopausal women results in a decreased risk of fracture (Ernster et al. 1988). Women who smoke and are on estrogen therapy may have reduced levels of estrogens in their blood compared with levels for nonsmoking women. Among women who smoked and were given high doses of estradiol, blood levels of estrone and estradiol were only one-half of those among nonsmokers (Jensen, Christiansen, Rodbro 1985). Increased hepatic metabolism of exogenous oral estrogen may result in lower estrogen levels among postmenopausal cigarette smokers.

Several case-control studies have evaluated the relationship between osteoporosis and cigarette smoking. Most find an increased risk of fractures among smokers. However, problems with study design, especially the potential effects of confounders such as obesity and age, have limited the interpretation of these studies, as have contradictory findings. For example, a large study of hip fractures among postmenopausal women in four Connecticut hospitals did not find any differences in risk between smokers and nonsmokers (Kreiger et al. 1982). A study in Iowa by Sowers (Sowers, Wallace, Lemke 1985) of 86 women aged 20 to 35 years did not find any relationship between forearm bone mineral mass and smoking during maximal bone mineralization. A study in Denmark (Jensen 1986) compared bone mineral content among 77 long-term smokers and 103 nonsmokers. Bone mineral content correlated with fat mass. For the same degrees of obesity, smokers did not have any lower level of bone mineral content than nonsmokers. The results of these studies suggest that the effect of smoking as a risk factor for osteoporosis and fracture among postmenopausal women may be primarily determined by the inverse relationship between smoking and obesity. It is possible that the early age of menopause among smokers may also contribute to the risk of osteoporosis.

Involuntary Smoking

The issue of involuntary smoking was not raised in the 1964 Surgeon General's Report. The first report of the Surgeon General to address the possible health effects of involuntary smoking was published in 1972 (US DHEW 1972). Over the ensuing 15 years, evidence on the adverse consequences of involuntary smoking began to amass, with several hundred papers being published. In 1986, the Surgeon General's Report (US DHHS 1986a) focused exclusively on this subject.

Nonsmoking adults exposed to ETS have a higher frequency of symptomology, such as eye irritation and upper respiratory symptoms (US DHHS 1986a). The relationship between lung cancer among nonsmokers and ETS has been documented in both case-control and longitudinal studies. Most of these studies have measured the increased risk of lung cancer among nonsmoking women, usually wives exposed to their husbands' tobacco smoke. A 1.3-fold increased risk of lung cancer has been estimated from these studies and is consistent with the amount of exposure to carcinogens from

ETS (US DHHS 1986a), the duration of exposure, and the differences in the distribution of potential carcinogens between sidestream and mainstream smoke.

The 1986 Surgeon General's Report on involuntary smoking concluded (US DHHS 1986a):

1. Involuntary smoking is a cause of disease, including lung cancer, in healthy nonsmokers.
2. The children of parents who smoke compared with the children of nonsmoking parents have an increased frequency of respiratory infections, increased respiratory symptoms, and slightly smaller rates of increase in lung function as the lung matures.
3. The simple separation of smokers and nonsmokers within the same airspace may reduce, but does not eliminate, the exposure of nonsmokers to ETS.

Another major review on involuntary smoking was released in 1986 by the National Research Council (NRC). This report concluded that the risk of lung cancer is approximately 30 percent higher for nonsmoking spouses of smokers than it is for nonsmoking spouses of nonsmokers (NRC 1986).

Since release of the 1986 Surgeon General's Report, five additional studies examining ETS exposure and lung cancer in nonsmokers have been published (Brownson et al. 1987; Dalager et al. 1986; Humble, Samet, Pathak 1987; Gao et al. 1987; Pershagen, Hrubec, Svensson 1987). All five noted a correlation between ETS exposure and lung cancer among nonsmokers. Thus, of the 16 epidemiologic studies in the scientific literature, 14 have noted a positive association.

Smokeless Tobacco

In 1979 the Surgeon General's Report included, for the first time, a review of the health consequences of using smokeless tobacco (snuff and chewing tobacco) (US DHEW 1979). In 1986, a special Surgeon General's Report, *The Health Consequences of Using Smokeless Tobacco* (US DHHS 1986b), reviewed smokeless tobacco in depth and concluded that it can cause cancer in humans. The relationship between smokeless tobacco use and cancer is strongest for the use of snuff and for cancer of the oral cavity. Smokeless tobacco can also cause oral leukoplakia, which may progress to neoplastic transformation with continued use of smokeless tobacco.

Addiction to Smoking

The 1964 Surgeon General's Report referred to tobacco use as habituating. Fifteen years later, the 1979 Report concluded that smoking was "the prototypical substance abuse dependency" (US DHEW 1979). The entire 1988 Report (US DHHS 1988) was dedicated to an exhaustive review of tobacco use as an addiction. The 1988 Report concluded:

1. Cigarettes and other forms of tobacco are addicting.
2. Nicotine is the drug in tobacco that causes addiction.
3. The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin or cocaine.

These findings are discussed in greater detail in Part II of Chapter 5 on determinants of smoking behavior.

PART II. THE PHYSICOCHEMICAL NATURE OF TOBACCO

The 1964 Surgeon General's Report on Smoking and Health (US PHS 1964) gave impetus to intensified investigations on the physicochemical nature and composition of tobacco smoke and the identification of biologically active agents in tobacco and tobacco smoke and their modes of action.

In 1936 Bruckner listed 120 known components in tobacco smoke. This number grew to about 450 in 1959 (Johnstone and Plimmer 1959), to about 950 in 1968 (Stedman 1968), to 3,875 in 1982 (Dube and Green 1982), and to 3,996 in 1988 (Roberts 1988). Today, the estimated number of known compounds in tobacco smoke exceeds 4,000, including some that are pharmacologically active, toxic, mutagenic, or carcinogenic (US DHEW 1979; US DHHS 1983). Such diverse biological effects of cigarette smoke constituents provide a framework for understanding the multiple adverse consequences of smoking.

Since about 1960, both the composition of cigarette tobacco and the components and shape of the cigarette itself have undergone significant changes that effected reductions in standardized measurements of tar, nicotine, and other toxic agents in the smoke (Norman 1982). Perhaps the greatest advances have been made in understanding the pharmacology and toxicology of nicotine (Benowitz 1986; US DHHS 1988) and in delineating the nature and mode of action of the major carcinogens in tobacco smoke (US DHHS 1982; Hoffmann and Hecht, 1989).

Processed, unadulterated tobacco contains at least 2,550 known compounds (Dube and Green 1982). The bulk of the dried tobacco consists of carbohydrates and proteins. Other important constituents are alkaloids (0.5 to 5 percent), with nicotine as the predominant compound (90 to 95 percent of total alkaloids), and terpenes (0.1 to 3 percent), polyphenols (0.5 to 4.5 percent), phytosterols (0.1 to 2.5 percent), carboxylic acids (0.1 to 0.7 percent), alkanes (0.1 to 0.4 percent), and alkali nitrates (0.01 to 5 percent). In addition, tobacco contains traces of aromatic hydrocarbons, aldehydes, ketones, amines, nitriles, N- and O-heterocyclic compounds, pesticides, and more than 30 metallic compounds (Wynder and Hoffmann 1967; US DHEW 1979).

The composition of the processed tobacco in cigarettes influences the chemistry and toxicity of the smoke. Cigarettes manufactured in the United States are made with blends of bright, burley, and oriental tobaccos that generate weakly acidic mainstream smoke (pH 5.5 to 6.2) in which nicotine occurs in protonated form in the particulate matter. The sidestream smoke (SS) of these cigarettes is neutral to alkaline (pH 6.5 to 8.0), and part of the nicotine in SS is present in unprotonated form in the vapor phase (Brunnemann and Hoffmann 1974). These observations are important because unprotonated nicotine is readily absorbed through the buccal mucosa (US DHHS 1988).

The 400 to 500 mg of mainstream smoke (MS) freshly emerging from the mouthpiece of a cigarette is an aerosol containing about 10^{10} particles per mL; these range in diameter from 0.1 to 1.0 μm (mean diameter 0.2 μm) and are dispersed in a vapor phase (Ingebrethsen 1986). About 95 percent of the MS effluents of a nonfilter cigarette are composed of 400 to 500 individual gaseous compounds with nitrogen, oxygen, and

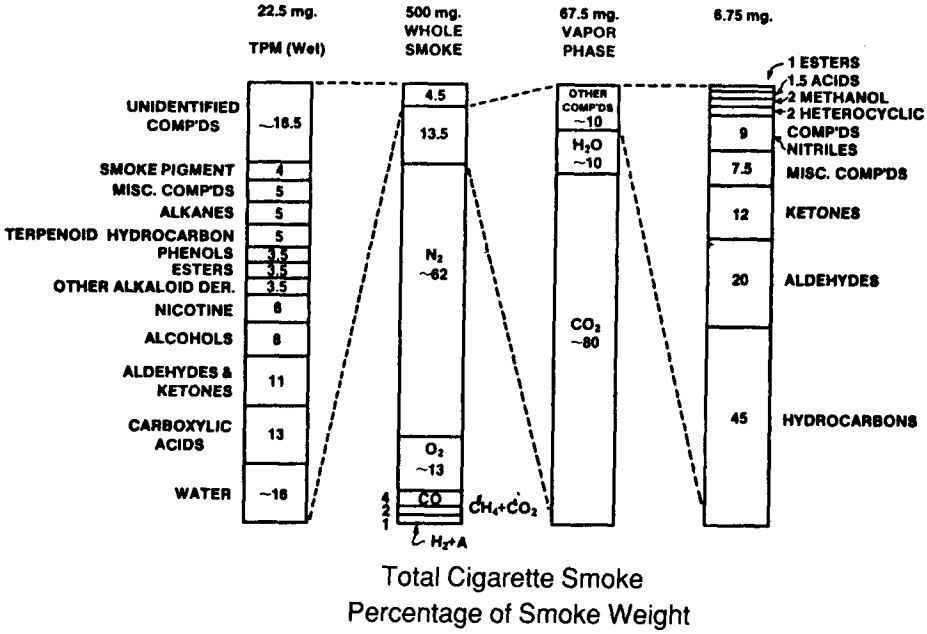

FIGURE 13.—Composition of cigarette mainstream smoke

SOURCE: Dube and Green (1982).

carbon dioxide as major constituents; the particulate matter of MS contains at least 3,500 individual compounds (Figure 13; Dube and Green 1982).

Like all organic combustion products, tobacco smoke contains free radicals, highly reactive oxygen- and carbon-centered types in the vapor phase, and relatively stable radicals in the particulate phase. The principal of the latter appears to be a quinone/hydroquinone complex capable of reducing molecular oxygen to superoxide, and, eventually, to hydrogen peroxide and hydroxyl radicals (Nakayama, Kodama, Nagata 1984; Church and Pryor 1985).

For chemical analysis, the smoke is arbitrarily separated into vapor and particulate phases. Those smoke components of which more than 50 percent appear in the vapor phase of fresh MS are considered volatile smoke constituents; all others are particulate phase components (Figure 13). Tables 5 and 6 list the major types of components identified and their estimated concentration in the smoke of one cigarette (US DHHS 1982; Hoffmann and Hecht 1989). The quantitative data presented here were obtained by machine smoking of cigarettes under standardized laboratory conditions using the method of the Federal Trade Commission (Pillsbury et al. 1969); therefore, the data do not fully reflect the human setting. This applies especially to smokers of low-yield cigarettes who tend to compensate for the low nicotine delivery by drawing smoke more intensely and inhaling more deeply (US DHHS 1988).

Table 6 does not contain information about the nature and concentration of at least 30 metals in the smoke. These compounds are not listed because less than I percent of the metals in tobacco are transferred into the smoke and constitute together only <=80 µg/g(Jenkins, Goldey, Williamson 1985). Tables 5 and 6 also lack descriptions of the

TABLE 5--Major constituents of the vapor phase of the mainstream smoke of nonfilter cigarettes

Compound[a]	Concentration/cigarette
Nitrogen	280-320 mg (56-64%[b])
Oxygen	50-70 mg (11-14%[b])
Carbon dioxide	45-65 mg (9-13%[b])
Carbon monoxide	14-23 mg (2.8-4.6%[b])
Water	7-12 mg (1.4-2.4%[b])
Argon	5mg (1.0%[b])
Hydrogen	0.5-1.0 mg
Ammonia	10-130 µg
Nitrogen oxides (NO_x)	100-600 µg
Hydrogen cyanide	400-500 µg
Hydrogen sulfide	20-90 µg
Methane	1.0-2.0 mg
Other volatile alkanes (20)	1.0-.16 mg[c]
Volatile alkenes (16)	0.4-0.5mg
Isoprene	0.2-0.4mg
Butadiene	25-40µg
Acetylene	20-35µg
Benzene	12-50µg
Toluene	20-60µg
Styrene	10µg
Other volatile aromatic hydrocarbons (29)	15-30µg
Formic acid	200-600 µg
Acetic acid	300-1,700 µg
Propionic acid	100-300 µg
Methyl formate	20-30 µg
Other volatile acids (6)	5-10 µg[c]
Formaldehyde	20-100 µg
Acetaldehyde	400-1,400 µg
Acrolein	60-140 µg

TABLE5.--Continued

Compound[a]	Concentration/cigarette
Other volatile aldehydes (6)	80-140 µg
Acetone	100-650 µg
Other volatile ketones (3)	50-100 µg
Methanol	80-180 µg
Other volatile alcohols (7)	10-30 µg[c]
Acetonitrile	100-150 µg
Other volatile nitriles (I0)	50-80 µgc
Furan	20-40 µg
Other volatile furans (4)	45-125 µg[c]
Pyridine	20-200 µg
Picolines (3)	15-80 µg
3-Vinylpyridine	10-30 µg
Other volatile pyridines (25)	20-50 µg[c]
Pyrrole	0.1-10 µg
Pyrrolidine	10-18 µg
N-Methylpyrrolidine	2.0-3.0 µg
Volatile pyrazines (18)	3.0-8.0 µg
Methylamine	4-10 µg
Other aliphatic amines (32)	3-10 µg

[a]Number in parenthese represent individual compounds identified in a given group.
[b]Percent of total effluent.
[c]Estimate.
SOURCE: Hoffmann and Hecht (1989).

chemical nature and concentrations in cigarette smoke of agricultural chemicals and pesticides, which originate from the residues of such compounds in tobacco. There are many variations in the qualitative and quantitative aspects relative to such agents in tobacco from region to region and from year to year. Overall, the use of agricultural chemicals has also been greatly reduced (Wittekindt 1985). Nevertheless, it is fairly certain that commercial tobaccos contain up to a few parts per million of DDT, DDD,

TABLE 6.--Major constituents of the particulate matter of the mainstream smoke of nonfilter cigarettes

Compound[a]	µg/cigarette
Nicotine	1,000-3,000
Nornicotine	50-150
Anatabine	5-15
Anabasine	5-12
Other tobacco alkaloids (17)	NA
Bipyridyls (4)	10-10
n-Hentriacontane ($n\text{-}C_{31}H_{64}$)	100
Total nonvolatile hydrocarbons (45)[b]	300-400[b]
Naphthalene	2-4
Other naphthalenes (23)	3-6[b]
Phenanthrenes (7)	0.2-0.4[b]
Anthracenes (5)	0.05-0.1[b]
Fluorenes (7)	0.6-1.0 [b]
Pyrenes (6)	0.3-0.5[b]
Fluoranthenes (5)	0.3-0.45[b]
Carcinogenic polynuclear aromatic hydrocarbons (11)[c]	0.1-0.25
Phenol	80-160
Other phenols (45)[b]	60-180[b]
Catechol	200-400
Other catechols (4)	100-200[b]
Other dihydroxybenzenes (10)	200-400[b]
Scopoletin	15-30
Other polyphenols (8)[b]	NA
Cyclotenes (10)b	40-70[b]
Quinones (7)	0.5
Solanesol	600-1,000

TABLE 6.--Continued

Compound[a]	µg/cigarette
Neophytadienes (4)	200-350
Limonene	30-60
Other terpenes (200-250)[b]	NA
Palmitic acid	100-150
Stearic acid	50-75
Oleic acid	40-110
Linoleic acid	60-150
Linolenic acid	150-250
Lactic acid	60-80
Indole	10-15
Skatole	12-16
Other indoles (13)	NA
Quinolines (7)	2-4
Other N-heterocyclic hydrocarbons (55)	NA
Benzofurans (4)	200-300
Other O-heterocyclic hydrocarbons (42)	NA
Stigmasterol	40-70
Sitosterol	30-40
Campesterol	20-30
Cholesterol	10-20
Aniline	0.36
Toluidines	0.23
Other aromatic amines (12)	0.25
Tobacco-specific N-nitrosamines (4)[c]	0.34-2.7
Glycerol	120

NOTE: NA, not available.
[a]Numbers in parentheses represent individual compounds identified in a given group.
[b]Estimate.
[c]See Table 7 for details.
SOURCE: Hoffmann and Hecht (1989).

and maleic hydrazide; fewer than 20 percent of these contaminants are transferred into the smoke stream.

The 1964 Surgeon General's Report listed five polynuclear aromatic hydrocarbons (PAHs) and three N-heterocyclic hydrocarbons as known carcinogenic smoke constituents (US PHS 1964). By the criteria for carcinogenicity of chemicals as set by the International Agency for Research on Cancer (1986), the carcinogens identified to date in tobacco smoke include 11 PAHs, 4 N-heterocyclic hydrocarbons, 9 N-nitrosamines, 3 aromatic amines, 3 aldehydes, 6 volatile carcinogens, 6 inorganic compounds, and the radioelement polonium-210 (Table 7; Hoffmann and Hecht 1989).

The Changing Cigarette

As discussed in Part I, epidemiologic studies have documented a dose-response relationship between the number of cigarettes smoked and the development of cancer of the lung, larynx, oral cavity, esophagus, pancreas, bladder, and kidney (US DHHS 1982; IARC 1986). Bioassays for tumorigenicity with whole smoke and with tar have also demonstrated a dose-response relationship (US DHHS 1982). As tar and nicotine yields in cigarette smoke gradually declined, other toxic and tumorigenic agents, such as CO, volatile N-nitrosamines, and carcinogenic PAHs, were also successfully reduced (Hoffmann, Tso, Gori 1980; Hoffmann et al. 1984; US DHHS 1981). However, it was soon realized that the smoker of low-yield cigarettes tended to compensate for reduced nicotine delivery by intensified smoking (US DHHS 1988), and therefore exposure may not actually have been lowered. Based on values generated by smoking machines under standardized conditions, Figure 14 shows the reduction in sales-weighted tar and nicotine delivery of the average U.S. cigarette. Arrows in the graph point to the introduction of technical changes in the manufacture of cigarettes at various times. These changes have influenced the machine-measured sales-weighted average nicotine and tar deliveries (Norman 1982). Technical issues in the machine measurements of delivered tar and nicotine yields also arose during 1982; modifications of the testing procedure were suggested (Federal Trade Commission 1984). The data shown in Figure 14 are based on the consistent testing procedures. Since 1981, the tar delivery of U.S. cigarettes has averaged between 13.0 and 12.7 mg, while nicotine delivery has remained stable at 0.9 mg per cigarette. (See Chapter 5, Table 26.) In the smoke of popular U.S. low-yield cigarettes, the reduction of nicotine, the primary pharmacologic factor in tobacco addiction (US DHHS 1988), has not occurred to the same extent as has the reduction of tar. The same development has been observed with cigarettes in the United Kingdom (Jarvis and Russell 1985).

Some modifications in the makeup of commercial cigarettes have led to a selective reduction of toxic and tumorigenic agents. Filter tips of cellulose acetate, the most common cigarette filter material, can selectively remove phenols and volatile N-nitrosamines from the smoke stream. Perforated filter tips selectively reduce CO and hydrogen cyanide (HCN) levels, and charcoal filters may selectively reduce volatile aldehydes and HCN. The incorporation into the tobacco blend of reconstituted tobacco sheets, expanded tobacco, and tobacco ribs has also contributed to a selective reduction of PAHs in cigarette smoke. The incorporation of ribs and stems and the utiliza-

TABLE 7.--Tumorigenic agents in tobacco and tobacco smoke

Compounds	Processed tobacco (per gram)	Mainstream (per cigarette)	Evidence for IARC evaluation of carcinogenicity	
			In lab animals	In humans
PAH				
Benz(a)anthracene		20-70 ng	Sufficient	NA
Benzo(b)fluoranthene		4-22 ng	Sufficient	NA
Benzo(j)fluoranthene		6-21 ng	Sufficient	NA
Benzo(k)fluoranthene		6-12 ng	Sufficient	NA
Benzo(a)pyrene	0.1-90 ng	20-40 ng	Sufficient	Probable
Chrysene		40-60 ng	Sufficient	NA
Dibenz(a,h)anthracene		4 ng	Sufficient	NA
Dibenzo(a,1)pyrene		1.7-3.2 ng	Sufficient	NA
Dibenzo(a,1)pyrene		Present	Sufficient	NA
Indeno(1,2,3-c,d)pyrene		4-20 ng	Sufficient	NA
5-Methylchrysene		0.6 ng	Sufficient	NA
Aza-arenes				
Quinoline		1-2 µg	NA	NA
Dibenz(a,h)acridine		0.1ng	Sufficient	NA
Dibenz(aj)acridine		3-10 ng	Sufficient	NA
7H-Dibenzo(c,g)carbazole		0.7 ng	Sufficient	NA
N-Nitrosamines				
N-Nitrosodimethylamine	ND-215 ng	0.1-180 ng	Sufficient	NA
N-Nitrosoethyl methylamine		3 -13 ng	Sufficient	NA
N-Nitrosodiethylamine		ND-25 ng	Sufficient	NA
N-Nitrosopyrrolidine	ND-360 ng	1.5-110 ng	Sufficient	NA
N-Nitrosodiethanolamine	ND-6,900 ng	ND-36 ng	Sufficient	NA
N'-Nitrosonomicotine	0.3-89 µg	0.12-3.7 µg	Sufficient	NA
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone	0.2-7 µg	0.08-0.77 µg	Sufficient	NA
N'-Nitrosoanabasine	0.01-1.9 µg	0.14-4.6 µg	Limited	NA
N-Nitrosomorpholine	ND-690 ng		Sufficient	NA

TABLE7.--Continued

Compounds	Processed tobacco (per gram)	Mainstream Smoke (per cigarette)	Evidence for IARC evaluation of carcinogenicity	
			In lab animals	In humans
Aromatic amines				
2-Toluidine		30-200 ng	Sufficient	Inadequate
2-Naphthylamine		1-22 ng	Sufficient	Sufficient
4-Aminobiphenyl		2-5 ng	Sufficient	Sufficient
Aldehydes				
Formaldehyde[a]	1.6-7.4 µg	70-100 µg[a]	Sufficient	NA
Acetaldehyde[a]	1.4-7.4 mg	18-1,400 mg[a]	Sufficient	NA
Crotonaldehyde	0.2-2.4 µg	10-20 µg	NA	NA
Miscellaneous organic compounds				
Benzene		12-48 µg	Sufficient	Sufficient
Acrylonitrile		3.2-15 µg	Sufficient	Limited
1,1-Dimethylhydrazine	60-147ug		Sufficient	NA
2-Nitropropane		0.73-1.21 µg	Sufficient	NA
Ethylcarbamate	310-375ng	20-38 ng	Sufficient	NA
Vinylchloride		1-16 ng	Sufficient	Sufficient
Inorganic compounds				
Hydrazine	14-51ng	24-43 ng	Sufficient	Inadequate
Arsenic	500-900 ng	40-120 ng	Inadequate	Sufficient
Nickel	2,000-6,000 ng	0-600 ng	Sufficient	Limited
Chromium	1000-2,000 ng	4-70 ng	Sufficient	Sufficient
Cadmium	1,300-1,600 ng	41-62 ng	Sufficient	Limited
Lead	8-10ug		Sufficient	Inadequate
Polonium-210	0.2-1.2pCi	0.03-1.0 pCi	NA	NA

NOTE: ND, no data; NA, evaluation has not been done by IARC.

[a]The Fourth Report of the Independent Scientific Committee on "Smoking and Health" (1988) published values for the 14 leading U.K. cigarettes in 1986 (51.4 percent of the market) of 20-105 µg/cigarette (mean, 59 ug) for formaldehyde and 550-1,150 µg/cigarette (mean, 910 µg) for acetaldehyde.

SOURCE: Hoffmann and Hecht (1989).

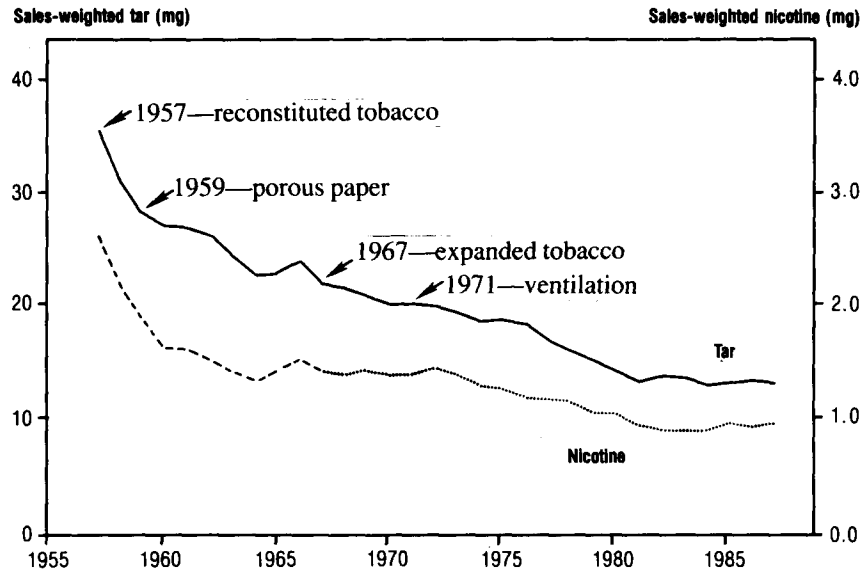

FIGURE 14.—"Tar" and nicotine content of U.S. cigarettes, sales-weighted average basis, 1957–87

NOTE: Nicotine values for 1957–67 are estimates.

SOURCE: 1957–67, Wakeham (1976), fourth-quarter estimates for each year; 1968–81, FTC (1984); 1982–87, derived from FTC data tape of annual cigarette company submissions to the FTC. This database is the same as that used for the ongoing FTC tobacco report series. Since 1981, these reports have not listed the sales-weighted tar average. Historical events are noted in R. J. Reynolds (1988).

tion of more burley varieties in the tobacco blend have led to an increase in the nitrate content of the U.S. blended cigarette from 0.5 percent to between 1.2 to 1.5 percent. This development brought about a reduction of the smoke yields of tar, phenols, and PAHs, but has caused an increase of the nitrogen oxides in the smoke and thus has increased the potential for N-nitrosamine formation (US DHHS 1981, 1982; Hoffmann et al. 1984). The development of the low-yield cigarette has also necessitated an enrichment of the flavor "bouquet" in the smoke either by tobacco selection or by addition of natural or synthetic flavor compounds. These facts and the practice of smoking low-yield cigarettes more intensely make it difficult to evaluate whether these new types of cigarettes are in fact less hazardous to the smoker (see Chapter 8). Changes in the market share of filtered cigarettes, lower yield cigarettes, mentholated cigarettes, and longer cigarettes are presented in Chapter 5.

Environmental Tobacco Smoke

SS is the smoke generated during smoldering of tobacco products between puffs. When it is obtained under standard laboratory conditions, undiluted SS contains far higher amounts of toxic and tumorigenic agents than MS, which is drawn puff by puff through the unlit end of the cigarette. Table 8 presents data for those toxic agents in SS that are known carcinogens, tumor promoters, and cocarcinogens. The release of volatile N-nitrosamines and aromatic amines into the SS is remarkably higher than that into MS (US DHHS 1988; Guerin 1987). Whereas filter tips, especially perforated

TABLE 8.--Some toxic and tumorigenic agents in undiluted cigarette sidestream smoke

Compound	Type of toxicity	Amount in sidestream smoke (per cigarette)	Amount in sidestream smoke/ amount in mainstream smoke
Vapor phase			
Carbon monoxide	T	26.8-61 mg	2.5-14.9
Carbonyl sulfide	T	2-3 ug	0.03-0.13
Benzene	C	400-40 µg	8-10
Formaldehyde	C	1.500 µg	50
3-Vinylpyridine	SC	300-450 µg	24-34
Hydrogen cyanide	T	14-110 µg	0.06-0.4
Hydrazine	C	90 ng	3
Nitrogen oxides (NO_x)	T	500-2,000 µg	3.7-12.8
N-Nitrosodimethylamine	C	200-1,040 ng	20-130
N-Nitrosopyrrolidine	C	30-390 ng	6-120
Particulate phase			
Tar	C	14-30 mg	1.1-15.7
Nicotine	T	2.1-46 mg	1.3-21
Phenol	TP	70-250 µg	1.3-3.0
Catechol	CoC	58-290 µg	0.67-12.8
o-Toluidine	C	3 µg	18.7
2-Naphtylamine	C	70 ng	39
4-Aminobiphenyl	C	140 ng	31
Benz(a)anthracene	C	40-200 ng	2-4
Benzo(a)pyrene	C	40-70 ng	2.5-20
Quinoline	C	15-20 µg	8-11
NNN	C	0.15-1.7 µg	0.5-5.0
NNK	C	0.2-1.4 µg	1.0-22
N-Nitrosodiethanolamine	C	43 ng	1.2
Cadmium	C	0.72 µg	7.2
Nickel	C	0.2-2.5 µg	13-30
Polonium-210	C	0.5-1.6 pCi	1.06-3.7

NOTE: C, carcinogenic; CoC, cocarcinogenic: SC, suspected carcinogen; T, toxic; TP, tumor promoter; NNN, N'-Nitrosonomicotine;NNK,4-(methylnitrosamino)-(3-pyridyl)-1-butanone.
SOURCE: Hoffmann and Hecht (1989).

ones, can significantly reduce the concentration of toxic and tumorigenic agents in MS, they have no reducing effect on the agents emitted into the SS (Adams, O'Mara-Adams, Hoffmann 1987).

SS is the major source of ETS. The smoke diffusing through the cigarette paper, the smoke emerging from the burning cone during active smoking, and that portion of MS that is exhaled also contribute to ETS. Table 9 presents some data for toxic agents resulting from tobacco combustion in indoor environments (US DHHS 1988; Hoffmann and Hecht 1989). The concentrations of toxic agents in ETS appear low in comparison with their levels in undiluted cigarette MS. With regard to exposure factors, one needs to take into account the fact that the active inhalation of MS is limited to the time it takes to smoke each cigarette, whereas the inhalation of ETS is constant over several hours spent in the polluted environment. This is reflected in the results of measurements of the uptake of nicotine by active and passive smokers (US DHHS 1988).

Smokeless Tobacco

As noted above, the special Report of the Surgeon General, *The Health Consequences of Using Smokeless Tobacco,* has shown that tobacco chewers and snuff dippers face an increased risk for cancer of the oral cavity (US DHHS 1986b). In the United States the four primary smokeless tobacco types are plug tobacco, loose leaf tobacco, twist tobacco, and snuff.

The composition of processed, unadulterated tobacco has been discussed. Chewing tobacco and snuff are made with various flavor additives (LaVoie et al. 1989). It is of special significance that the preparation of smokeless tobacco products, which entails curing, fermentation, and aging, occurs under conditions favoring the formation of tobacco-specific N-nitrosamines (TSNAs) from nicotine and other tobacco alkaloids such as nornicotine, anatabine, and anabasine (Figure 15). Of the six identified TSNAs in smokeless tobacco, N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are strong carcinogens in mice, rats, and hamsters, inducing benign and malignant tumors of the oral cavity, nasal cavity, esophagus, lung, liver, and pancreas (Hecht and Hoffmann 1988; Rivenson et al. 1988). Table 10 presents chemical-analytical data for TSNAs in U.S. smokeless tobacco products (Hoffmann and Hecht 1988). The concentrations of carcinogenic nitrosamines in smokeless tobacco exceed those in other consumer products by at least 2 orders of magnitude (US DHHS 1986b). During tobacco chewing and snuff dipping, additional amounts of carcinogenic TSNAs are most likely also formed endogenously in the oral cavity (Hoffmann and Hecht 1988). Carcinogenic TSNAs have been regarded as a major factor for the association of snuff-dipping with oral cancer in humans (Craddock 1983).

Other carcinogens identified in smokeless tobacco are volatile nitrosamines (N-nitrosodimethylamine, <=215 ppb), N-nitrosomorpholine (<=40 ppb), N-nitrosodiethylamine (<=6,800 ppb), formaldehyde (<=7,000 ppb), crotonaldehyde (<=2,400 ppb), and benzo(a)pyrene (<=90 ppb), as well as traces of the radioelement polonium-210 (<=0.6 pCi/g) (US DHHS 1986; Hoffmann et al. 1987; Chamberlain, Schlotzhauer, Chortyk 1988).

TABLE 9.--Some toxic and tumorigenic agents in indoor environments polluted by tobacco smoke

Pollutant	Location	Concentration/m^3
Nitric oxide	Workrooms	50-440 µg
	Restaurants	17-270 µg
	Bars	80-520 µg
	Cafeterias	2.5-48 µg
Nitrogen dioxide	Workrooms	68-410 µg
	Restaurants	40-190 µg
	Bars	2-116 µg
	Cafeterias	67-200 µg
Hydrogen cyanide	Living rooms	8-122 µg
Benzene	Public places	20-317 µg
Formaldehyde	Living rooms	23-50 µg
Acrolein	Public places	30-120 µg
Acetone	Public places	360-5,800 µg
Phenols (volatile)	Coffee houses	7.4-11.5 ng
N-Nitrosodimethylamine	Restaurants, public places	0-240 ng
N-Nitrosodiethylamine	Restaurants, public places	0-200 ng
Nicotine	Public places	1-6 µg
	Restaurants	3-10 µg
	Workrooms	1-13.8 µg
Benzo(a)pyrene	Restaurants, Public places	3.3-23.4 ng

SOURCE: Hoffmann and Hecht (1989).

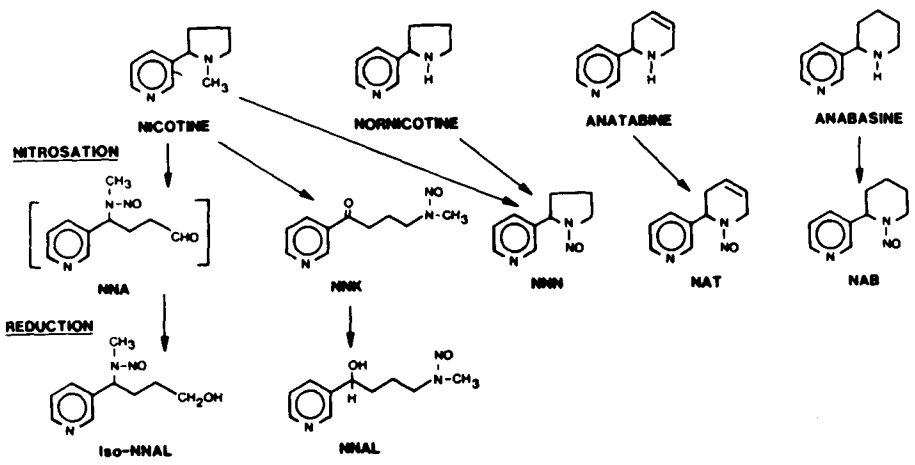

FIGURE 15.—Formation of tobacco-specific N-nitrosamines

TABLE 10.—Tobacco-specific N-nitrosamines in U.S. smokeless tobacco (ppb)

Product	NNN	NNK	NAT	NAB
Loose leaf tobacco	670–8,200 (6[a])	380 (1)	2,300 (1)	140 (1)
Plug tobacco	3,400–4,300 (3)			
Snuff—moist	3,120–135,000 (26)	100–13,600 (25)	1,340–339,000 (20)	10–6,700 (16)
Snuff—dry	9,000–52,000 (3)	1,800–13,000 (3)	18,000–38,000 (3)	60–60,000 (3)

NOTE: NNN, N′-Nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NAT, N′-nitrosoanatabine; NAB, N′-nitrosoanabasine.

[a]Number in parentheses is the number of samples analyzed.

SOURCE: Hoffmann and Hecht (1988).

Toxicity and Carcinogenicity of Tobacco Smoke

Undiluted tobacco smoke is too toxic to be tolerated by laboratory animals primarily because of the acute toxic effects of CO. CO in cigarette smoke increases with ascending puff number from 2 to 5 volume percent (the average CO content of cigarette smoke is 3.5 to 4.5 volume percent). The acute toxicity of tobacco smoke is also due to HCN. nicotine. and volatile aldehydes. In vitro short-term exposure to cigarette smoke causes ciliastasis, an effect primarily attributable to HCN (300 to 500 µg/cigarette) and volatile aldehydes (500 to 2,000 µg/cigarette). The long-term exposure of laboratory animals to diluted cigarette smoke causes impairment of mucociliary

clearance, mucus hypersecretion, and epithelial lesions. Cigarette smoke constituents responsible for this effect are both the gas phase, primarily HCN and volatile aldehydes, and the particulate phase (US DHEW 1979; US DHHS 1984).

Long-term inhalation of diluted cigarette smoke by mice has resulted in adenomas and adenocarcinomas of the lung, whereas such inhalation in rats has only led to a few isolated tumors of the lung. In Syrian golden hamsters, long-term smoke inhalation studies have regularly induced benign and malignant tumors of the larynx and only a few lung tumors. These observations strongly suggest, and studies of particulate deposition and determination of carboxyhemoglobin (COHb) and nicotine-cotinine in the blood of the smoke-exposed animals have confirmed, that laboratory animals do not inhale the smoke deeply. Intratracheal instillation of cigarette tar and one of its fractions has resulted in lung tumors, including bronchogenic carcinomas (Mohr and Reznik 1978; Dalbey et al. 1980; US DHHS 1982).

The particulate matter (more often called "tar") suspended in organic solvents has induced carcinoma in the rat after subcutaneous injection and benign and malignant tumors in the skin of mice and rabbits after topical application. The major tumor initiators reside in the PAH-enriched neutral subfractions, whereas the tumor promoters and cocarcinogens are found in the weakly acidic fraction as well as in the polaric neutral subfraction (Wynder and Hoffmann 1967; Mohr and Reznik 1978; US DHHS 1982; Hoffmann and Hecht 1988).

As discussed earlier, combined chemical-analytical studies have led to the identification of several organ-specific carcinogens in cigarette smoke. The diversity of these carcinogens and those identified as contact carcinogens may cause ambiguity as to which among them are most important. Table 11, which is based on extensive laboratory studies, lists the likely causative agents associated with the increased risk of cigarette smokers for cancer of the various organs (Hoffmann and Hecht 1988).

Nicotine

It is generally held that nicotine is the active pharmacologic agent in tobacco that determines the addictive behavior of the tobacco smoker (US DHHS 1988). Nicotine, together with CO, is also regarded as a major contributor to cigarette smokers' increased risk of cardiovascular disease (US DHHS 1983, 1988). In addition to nicotine, tobacco contains various other alkaloids, most of which are 3-pyridyl derivatives. In the blended U.S. cigarette, nicotine constitutes 85 to 95 percent of the total alkaloids. During the smoking of a nonfilter cigarette, about 15 percent of the nicotine appears in the MS, 35 to 40 percent appears in the SS, 15 to 20 percent is deposited in the butt, and the remainder is broken down into pyrolysis products. The major pyrolysis products of nicotine are CO, carbon dioxide, 3-vinylpyridine, 3-methylpyridine, pyridine, myosmine, and 2,3'-dipyridyl (US DHHS 1982).

As discussed earlier, the absorption of nicotine from tobacco smoke is pH dependent. When tobacco smoke reaches the small airways and alveoli of the lung, nicotine is rapidly absorbed. In chewing tobacco and snuff with their alkaline pH, nicotine is primarily absorbed through the mucous membranes of the oral cavity. Nicotine enters the blood and is rapidly transported to the brain, which has specific receptor sites for

TABLE 11.--Likely causative agents for tobacco-related cancers

Organ	Initiator or carcinogen	Enhancing agents
Lung, larynx	PAH	Catechol (cocarcinogen) Weakly acidic tumor promoters
	NNK	Acrolein, crotonaldehyde (?)
	Polonium-210 (minor factor), acetaldehyde, formaldehyde	
Esophagus	NNN	
Pancreas	NNK(?)	
Bladder	4-Aminobiphenyl 2-Naphthylamine	
Oral cavity (smoking)	PAH NNK. NNN	Ethanol
Oral cavity (snuff dipping)	NNK, NNN	Irritation (?) Herpes simplex (?)
	Polonium-210	

NOTE: PAH, polynuclear aromatic hydrocarbons; NNK, 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone; NNN, N'-Nitrosonomicotine.
SOURCE: Hoffmann and Hecht (1989).

the drug. The effects of nicotine on the central nervous system are associated with the development of tobacco dependence (US DHHS 1988).

Nicotine is metabolized primarily in the liver and, to a smaller extent, in the lung. About 10 to 15 percent of the absorbed nicotine is excreted unchanged in the urine. The primary metabolites of nicotine are cotinine and nicotine-N'-oxide. Cotinine is further metabolized extensively, with only 17 percent of it appearing unchanged in the urine (Benowitz 1986; Neurath et al. 1987; US DHHS 1988). Cotinine measurements in saliva, serum, or urine serve as an indicator for nicotine uptake by tobacco chewers, active smokers, and involuntary smokers. It takes 18 to 20 hr to eliminate one-half of the cotinine present in an active smoker through renal excretion; an involuntary smoker shows a considerably slower rate of elimination (Sepkovic, Haley, Hoffmann 1986; US DHHS 1988).

Biological Markers

Techniques for the determination of current and lifetime exposures to tobacco products include the examination of medical records and data from prospective and

case-control studies as well as the utilization of biological markers. The development of highly sensitive and reproducible methods has led to increased use of biological markers for uptake of tobacco smoke constituents.

Table 12 lists those biochemical markers that are currently used to determine exposure to tobacco smoke components after active inhalation of MS and also after involuntary uptake of ETS. Some of these markers are also the basis for measuring the transfer of smoke constituents from the maternal bloodstream to a developing fetus.

The tobacco-specific alkaloid nicotine and its major metabolite, cotinine, are most frequently used as serum and urine indicators of the uptake of tobacco smoke by active smokers and also to indicate ETS exposure in nonsmokers. Unlike CO, nicotine is not

TABLE 12.--Biochemical markers for the uptake of tobacco smoke

Smoke constituent	Biochemical marker	Substrate	Method	Sensitivity	Critical value[a]
Nicotine	Nicotine	Serum Urine	GC	1 ng/mL	0
		Serum Urine	RIA	0.2 ng/mL	0
	Cotinine	Saliva Serum Urine	GC	5 ng/mL	0
		Saliva Serum Urine	RIA	1 ng/mL	0
Carbon monoxide (CO)	COHb	Blood	Oximeter	±0.1%	0.9±0.7%
	CO	Exhaled air	GC	±1 ppm	5.6±2.7 ppm
Hydrogen cyanide (HCN)	Thiocyanate (SCN^-)	Saliva Serum Urine	Autoanalyzer (color reaction)	±5 µmol/L	100 µmol/L
Nitrogen oxides (NO_X)	Nitrosoproline	Urine	GC/TEA	±0.4 µg/L	2.0±1.5 µg/24hours
Ethylene ($CH_2=CH_2$)	Globin-adduct	Blood	GC	±5pmol/gHb	58±25 pmol/gHb
4-Aminobiphenyl	Globin-adduct	Blood	GC	?	<70pg/gHb
Tobacco-specific nitrosamines	Globin-adduct	Blood	GC	?	Not established

[a]Critical values, values measured in nonsmokers.

SOURCE: International Agency for Research on Cancer (1987).

only taken up by inhalation but also is absorbed through the mucous membranes in the oral cavity. Therefore, it is possible to determine user uptake of hydrophilic agents from chewing tobacco and snuff by means of nicotine-cotinine measurements. The analytical assessment of nicotine and cotinine in physiological fluids is done primarily by gas chromatography and radioimmunoassay (IARC 1986). Both methods are highly sensitive (between 0.2 and 5 ng/mL), and there is little or no interference by other smoke components. After environmental exposure, the average nicotine and cotinine levels in saliva, plasma, and urine of nonsmokers vary from 0.5 to 4.0 µg/mL, whereas the average amount of nicotine in the serum of cigarette smokers ranges from 15 to 40 µg/mL and lies between 500 and 2,000 µg/mL in saliva and urine. Cotinine concentration varies from 150 to 350 µg/mL in plasma, from 150 to 400 µg/mL in saliva, and can go up to 2,000 µg/mL in urine (Jarvis et al. 1984; US DHHS 1988). In snuff dippers and tobacco chewers, plasma nicotine levels were found between 3 to 22 µg/mL and plasma cotinine was 200 to 400 µg/mL (US DHHS 1986).

One of the oldest methods for estimating the inhalation of tobacco smoke is the determination of COHb in blood. Since some CO is endogenously formed, the background values for COHb in the blood of nonsmokers without occupational exposure to CO range from 0.5 to 1.5 percent (National Research Council 1977). Smoking only a few cigarettes per day elevates COHb levels to 2.0 percent. In a study of men aged 34 to 64 years, cigarette smokers had average COHb concentrations of 4.7 percent; cigar smokers, 2.9 percent; and pipe smokers, 2.2 percent (Wald et al. 1981; Wald and Ritchie 1984). The COHb values of nonsmokers after ETS exposure do not markedly exceed 1.5 percent; thus, COHb cannot serve as an indicator of exposure to ETS (NRC 1986). Since CO is only slowly released from the blood in the process of exhaling, the smoking intensity of a cigarette smoker can also be assessed by the analysis of CO in the exhaled breath. The critical value for CO, the value above that of a nonsmoker, is 5.6±2.7 ppm in exhaled breath; again this method is not applicable to the dosimetry of nonsmoker ETS exposures.

HCN, a major tobacco smoke constituent (>l00 µg/cigarette), is absorbed upon inhalation and is detoxified in the liver, yielding SCN^-. Since SCN^- can also originate from dietary intake, only values above 100µmol of SCN^- per L of serum as measured for cigarette smokers are meaningful for dosimetry of uptake. In general, the average cigarette smoker has SCN^- levels between 100 and 250 µmol/L of serum (US DHHS 1987).

A number of studies have clearly demonstrated that the mutagenic activity of the urine of cigarette smokers is higher than that of nonsmokers (IARC 1986). The most widely applied method for determining mutagenic activity of urine samples was developed by Yamasaki and Ames (1977), using a resin to concentrate the body fluid and, upon metabolic activation, measuring the mutagenic activity on bacterial tester strains TA98 and TA1538. In general, the urine of cigarette smokers exhibits at least twice the mutagenic activity of that measured in nonsmokers' urine.

In summary, there are several biochemical indicators that enable investigators to assay the uptake of tobacco smoke by individuals or by groups of individuals. Whereas analyses of exhaled CO, of COHb, and of SCN^- and nicotine-cotinine in saliva, serum, and urine are well suited for determining the smoking intensity of an active smoker,

only nicotine and cotinine determinations in serum and urine can also serve as indicators for the exposure of nonsmokers to ETS.

Summary

The 1964 Surgeon General's Report was a landmark study that reviewed and assessed the available epidemiologic, clinical, pathological, and experimental literature for evidence linking cigarette smoking to disease. The principal findings of that Report are summarized in Table 13. In men, cigarette smoking was found to increase overall mortality and to cause lung and laryngeal cancer. Several other important conclusions were also drawn (Table 13).

Since 1964, 20 reports of the Surgeon General (including this Report) have been released on tobacco and health that substantiate and strengthen the original conclusions of the 1964 Report. These reports have also established associations between smoking and disease in areas for which data did not exist, shed light on pathogenetic mechanisms of tobacco-related disease, and added scientific depth to areas mentioned only briefly in the 1964 Report.

A review of Table 13 allows the reader to survey quickly the state of knowledge on cigarette smoking and health in 1989 and to compare it with what was known in 1964. Of the 27 principal effects presented in Table 13, 13 were first noted in 1964; among those 13 effects, many have been strengthened since 1964. Recent reports of the Surgeon General have also covered important topics not even mentioned in the 1964 Report. For example, these reports have concluded that involuntary smoking can cause disease, including lung cancer, in healthy nonsmokers and that smokeless tobacco can cause oral cancer. The most recent Surgeon General's Report also concluded that the use of cigarettes and other forms of tobacco is addicting (US DHHS 1988).

Much progress has been made in understanding the physicochemical nature of tobacco smoke. Today, the estimated number of compounds in tobacco smoke exceeds 4,000, including some that are pharmacologically active, toxic, mutagenic, or carcinogenic. The diverse biological effects of tobacco smoke constituents provide a framework for understanding the multiple adverse consequences of smoking. For example, the identification of 43 different carcinogenic substances in tobacco smoke helps explain why cigarette smoking can cause cancer at different sites including the lung, larynx, oral cavity, and esophagus; why cigarette smoking is a contributory factor for the development of cancer at different sites including the bladder, kidney, and pancreas; and why cigarette smoking is associated with cancer of the stomach and uterine cervix.

The central role of cigarette smoking as a massive, preventable personal and public health problem can now be better appreciated. In the United States, it is a major cause of CHD, this country's most common cause of death; cigarette smoking is estimated to account for 21 percent of all CHD deaths. Cigarette smoking is the major cause of lung cancer, the most common cause of cancer death in the United States; smoking is estimated to account for 87 percent of lung cancer deaths and 30 percent of all cancer deaths. While lung cancer death rates for women who are nonsmokers have not increased since the early 1960s comparable death rates for women who smoke cigarettes have increased more than fourfold. In 1986, lung cancer and breast cancer were the

TABLE 13.--Summary of the principal effects of cigarette smoking

Effect first discussed in Surgeon General's Reports	Year first discussed in a Surgeon General's Report	Current knowledge in 1989
Mortality and morbidity		
Overall mortality, increased in men	1964	Overall mortality increased in men and women
Overall morbidity, increased	1967	Overall morbidity increased
Cardiovascular		
CHD, mortality increased in men	1964	A major cause of coronary heart disease in men and women
Cerebrovascular disease (stroke), mortality increased	1964	A cause of cerebrovascular disease (stroke)
Atherosclerotic aortic aneurysm, mortality increased	1967	Increased mortality from atherosclerotic aortic aneurysm
Atherosclerotic peripheral vascular disease, risk factor	1971	A cause and most important risk factor for atherosclerotic peripheral vascular disease
Cancer		
Lung cancer, the major cause in men	1964	The major cause of lung cancer in men and women
Laryngeal cancer, a cause in men	1964	The major cause of laryngeal cancer in men and women
Oral cancer (lip), a cause (pipe smoking)	1964	A major cause of cancer of the oral cavity (lip, tongue, mouth, pharynx)
Esophageal cancer, associated with	1964	A major cause of esophageal cancer
Bladder cancer, associated with	1964	A contributory factor for bladder cancer
Pancreatic cancer, increased mortality	1967	A contributory factor for pancreatic cancer
Renal cancer, increased mortality	1968	A contributory factor for renal cancer
Gastric cancer, associated with	1982	An association with gastric cancer
Cervical cancer, possible association with	1982	An association with cervical cancer

TABLE 13.--Continued

Effect first discussed in Surgeon General's Reports	Year first discussed in a Surgeon General's Report	Current knowledge in 1989
Pulmonary		
Chronic bronchitis, the major cause	1964	The major cause of chronic bronchitis
Emphysema, increased mortality	1964	The major cause of emphysema
Women		
Low-birthweight babies, associated with	1964	A cause of intrauterine growth retardation
Unsuccessful pregnancy, associated with	1980	A probable cause of unsuccessful pregnancies
Other effects		
Tobacco habit, related to psychological and social drives	1964	Cigarette smoking and other forms of tobacco use are addicting
Involuntary smoking, irritant effect	1972	A cause of disease, including lung cancer, in healthy nonsmokers
Peptic ulcer disease, associated with	1964	A probable cause of peptic ulcer disease
Occupational interactions, adverse	1971	Adverse occupational interactions that increase the risk of cancer
Alcohol interactions, adverse	1971	Adverse interactions with alcohol that increase the risk of cancer
Drug interactions, adverse	1979	Adverse drug interactions
Nonmalignant oral disease, associated with	1969	An association with nonmalignant oral disease
Smokeless tobacco, associated with oral cancer	1979	Smokeless tobacco is a cause of oral cancer

leading causes of cancer death in U.S. women, accounting for approximately equal numbers of cancer deaths. Cigarette smoking is the major cause of COPD, an effect that far outweighs all other factors; smoking is estimated to account for 82 percent of COPD deaths. (See Chapter 3.)

The 1964 Report of the Surgeon General stated that death rates from cerebrovascular disease (stroke) were increased in cigarette smokers compared with nonsmokers, but it drew no conclusions concerning causality. In the current 1989 Report, for the first time, cigarette smoking is cited as a cause of stroke, the third most common cause of death in the United States. Stopping smoking reduces the risk of stroke.

The effect of smoking on pregnancy was briefly mentioned in the 1964 Report. Many studies have subsequently shown that cigarette smoking causes fetal growth retardation and is a probable cause of unsuccessful pregnancies.

Table 13 summarizes other important smoking associations with several diseases, including atherosclerotic aortic aneurysm, atherosclerotic peripheral vascular disease, and peptic ulcer disease; it also includes occupational and alcohol-related interactions with smoking that increase the risk of cancer.

Finally, the reports of the Surgeon General have emphasized the benefits of quitting for smokers of all ages.

CONCLUSIONS

Part I. Health Consequences

1. The 1964 Surgeon General's Report concluded that cigarette smoking increases overall mortality in men, causes lung and laryngeal cancer in men, and causes chronic bronchitis. The Report also found significant associations between smoking and numerous other diseases.
2. Reports of the Surgeon General since 1964 have concluded that smoking increases mortality and morbidity in both men and women. Disease associations identified as causal since 1964 include coronary heart disease, atherosclerotic peripheral vascular disease, lung and laryngeal cancer in women, oral cancer, esophageal cancer, chronic obstructive pulmonary disease, intrauterine growth retardation, and low-birthweight babies.
3. Cigarette smoking is now considered to be a probable cause of unsuccessful pregnancies, increased infant mortality, and peptic ulcer disease; to be a contributing factor for cancer of the bladder, pancreas, and kidney; and to be associated with cancer of the stomach.
4. Accumulating research has elucidated the interaction effects of cigarette smoking with certain occupational exposures to increase the risk of cancer, with alcohol ingestion to increase the risk of cancer, and with selected medications to produce adverse effects.
5. A decade ago, the 1979 Report of the Surgeon General found smokeless tobacco to be associated with oral cancer. In 1986, the Surgeon General concluded that smokeless tobacco was a cause of this disease.

6. Research in the present decade has established that involuntary smoking is a cause of disease, including lung cancer, in healthy nonsmokers, and that the children of parents who smoke have an increased frequency of respiratory infections and symptoms.
7. In 1964, tobacco use was considered habituating. A substantial body of evidence accumulated since then, and summarized in the 1988 Surgeon General's Report, has established that cigarettes and other forms of tobacco are addicting. Given the prevalence of smoking, tobacco use is the Nation's most widespread form of drug dependency.
8. Studies dating from the 1950s have consistently documented the benefits of smoking cessation for smokers in all age groups.
9. Recent evidence, including that presented in this 1989 Report of the Surgeon General, documents that cigarette smoking is a cause of cerebrovascular disease (stroke) and is associated with cancer of the uterine cervix.

Part II. The Physicochemical Nature of Tobacco

1. The estimated number of compounds in tobacco smoke exceeds 4,000, including many that are pharmacologically active, toxic, mutagenic, and carcinogenic.
2. Forty-three carcinogens have been identified in tobacco smoke.
3. Carcinogenic tobacco-specific nitrosamines are found in high concentrations in smokeless tobacco.

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