1. Most of the experimental work in humans, animals, and tissues involving enzyme systems indicates that the dominant effect of smoking is enhanced drug disposition caused by induction of hepatic microsomal enzymes.

2. Tobacco smoke, a complex mixture of noxious materials, contains, among other compounds, enzyme inducers such as polycyclic aromatic hydrocarbons, nicotine, cadmium and some pesticides, acrolein and hydrogen cyanide.

3. The primary inducers are probably polynuclear aromatic hydrocarbons which are potent and persistent in tissues. While several of the hepatic microsomal drug-metabolizing enzymes are stimulated in smokers, this enhancement is unpredictable, and the effects of cigarette smoke on other potential rate-limiting disposition processes for drugs are largely unexplored.

4. Cigarette smoking alters the pharmacologic effects of drugs or their pharmacokinetics.

5. Tobacco smoke can induce the metabolism in humans of therapeutic agents, such as phenacetin, antipyrine, theophylline, caffeine, imipramine, pentazocine, and vitamin C; examples of drugs not affected by smoking include: diazepam meperidine, phenytoin, nortriptyline, warfarin, and ethanol.

6. Tobacco smoke can modify the clinical effects of drugs.

7. Marijuana smoking may produce reactions similar to tobacco smoking since enzyme induction is also stimulated by the polycyclic aromatic hydrocarbons in marijuana smoke.

8. A woman who both smokes and uses oral contraceptives has a greater risk for myocardial infarction.

9. There is a suggestion that smoking produces a more rapid decline in influenza antibody titers after natural infection or vaccination with influenza virus.

10. Cigarette smoking appears to increase the serum carcinoembryonic antigen level in otherwise healthy individuals.

11. No information is available to indicate that the increase in body burden of trace elements by smoking has toxic effects.

12. Since tobacco smoking does affect the values of a number of clinical laboratory tests in humans, the knowledge of an individual's smoking status is important for the interpretation of such tests. Cigarette smoking increases the number of leukocytes, the red cell mass, the levels of hemoglobin and carboxyhemoglobin, the hematocrit, the mean corpuscular volume, platelet aggregation, plasma viscosity, and tensile strength of the clot; cigarette smoking decreases the serum levels of creatinine, albumin, globulin (female smokers) and uric acid (male smokers). These revert to normal levels after cessation of smoking.

Other Forms of Tobacco Use

References have already been made to the relationships between other forms of tobacco use and a number of specific diseases and cancer sites. Special attention was given in the 1973 issue of *The Health Consequences of Smoking* to the role of pipes and cigars. This attention was particularly relevant inasmuch as the 1964 Report appeared to have influenced a transient increase in consumption of cigars and pipe tobacco due to the prevailing belief that pipes and cigars were "safe."

For the present report, the summary conclusions presented here refer to men only, since the use of pipes and cigars in the United States is limited almost exclusively to them.

It can be concluded that some risk exists from smoking cigars and pipes as they are currently used in the United States, but for most diseases this is small compared to the risk of smoking cigarettes as they are commonly used.

Overall Mortality

1. Overall mortality rates among pipe or cigar smokers are slightly higher than for nonsmokers.

2. Mortality rates among smokers of pipes, cigars, or both in combination with cigarettes are intermediate between the high rates of cigarette smokers and the lower rates of those who smoke only pipes or cigars.

3. Mortality associated with combinations of pipe and/or cigar and cigarette smoking is dependent upon the level of consumption and inhalation of each.

4. A dose-response relationship exists for the several forms of tobacco use and overall mortality in terms of amount smoked, degree of inhalation, duration of smoking, and age at initiation of smoking.

Cancer

1. Prospective studies have shown that mortality rates from cancer of the oral cavity, larynx, pharynx, and esophagus are approximately equal in users of cigars, pipes, and cigarettes.

2. Although several factors appear to be involved in cancer of the lip, pipe smoking alone or in combination with other forms of smoking is causally related to lip cancer.

3. Heavy alcohol consumption in combination with heavy smoking of pipes and cigars is associated with higher rates of oral cancer than for either alcohol consumption or heavy smoking of pipes or cigars alone. There is evidence that excessive alcohol consumption may increase the pipe and cigar smoker's risk for extrinsic laryngeal cancer. A distinct synergism with heavy alcohol intake exists in esophageal cancer.

4. Cigar and pipe smokers showed the same histological changes in the larynx and esophagus at autopsy as did cigarette smokers.

5. Pipe and cigar smokers have histological abnormalities of the lung at autopsy that are intermediate in degree between nonsmokers and cigarette smokers. Some categories of pathologic changes in cigar smokers are similar to those seen in cigarette smokers.

6. The risk of pipe and cigar smokers developing lung cancer is higher than for nonsmokers, but is lower than for cigarette smokers. In the updated prospective studies, the relative risks of lung cancer for cigar and pipe smoking ranged from 1.6 to 3.4 for cigars only and from 1.8 to 8.5 for pipe only.

7. A dose-response gradient has been shown to be present in some studies.

Tumorigenic Activity of Pipe and Cigar Smoke Condensates

1. Pipe and cigar tobacco condensates have a carcinogenic potential comparable to that of cigarette condensates.

2. The alkaline smoke from pipe and cigar tobacco is usually not inhaled, and there appears to be a lower level of exposure of the harmful components of smoke than is noted with the inhalation of cigarette smoke.

Cardiovascular Diseases

1. Pipe and cigar smokers experience a small increase in coronary heart disease mortality compared to nonsmokers.

2. Similarly, pipe and cigar smokers show slight excesses of cerebrovascular death rates over nonsmokers.

Non-Neoplastic Bronchopulmonary Disease

1. Pipe and cigar smokers experience mortality rates from chronic bronchitis and emphysema that are intermediate between cigarette smokers and nonsmokers.

2. Pipe and cigar smokers have significantly more respiratory symptoms such as cough, sputum production, breathlessness, and wheezing than nonsmokers. A dose-response gradient is noted.

3. Little difference in pulmonary function was noted for pipe and cigar smokers as compared to nonsmokers.

4. Pipe and cigar smokers had far less pulmonary pathology at autopsy than did cigarette smokers.

Peptic Ulcer Disease

1. Cigar and pipe smokers experience higher death rates from peptic ulcer than nonsmokers: these rates, based on prospective mortality studies, indicated higher rates for gastric ulcer than for duodenal ulcer.

2. Retrospective and cross-sectional studies failed to find an association between pipe smoking and peptic ulcer.

Snuff and Chewing Tobacco and Oral Lesions

Snuff and chewing tobacco have not been found to increase mortality (either overall or cause-specific) in the United States. Asian studies have found an association between tobacco chewing and leukoplakia as well as oral cancer. These differences between the American and Asian studies can partially be explained by nutritional factors but are confounded by other factors such as the use of other tobacco products along with the use of snuff and chewing tobacco in the United States.

Constituents of Tobacco Smoke

Extensive research has advanced the cultivation of tobacco varieties with commercially desirable characteristics. This research has also been directed toward precursor-product relationships among specific leaf tobacco components, agronomic characteristics, cigarette and smoke constituents, and biological responses involving 151 variables. Multivariate analysis has revealed that leaf characteristics serve as markers to predict individual smoke components. Thus, there is promise of modification for more desirable qualities and use of tobacco.

Smoke Formation

1. The lighted cigarette generates about 2,000 compounds by a variety of processes including hydrogenation pyrolysis, oxidation, decarboxylation, dehydration, chemical condensation, distillation, and sublimation.

2. Tobacco smoke has been separated into gas and particulate phases.

3. The gas phase components shown to produce undesirable effects include carbon monoxide, carbon dioxide, nitrogen oxides, ammonia, volatile N-nitrosamines, hydrogen cyanide, volatile sulfur compounds, nitriles and other nitrogen-containing compounds, volatile hydrocarbons, alcohols, aldehydes, and ketones.

4. The particulate phase consists generally of nicotine, water, and "tar". "Tar," which is the total particulate matter after subtracting moisture and nicotine, consists primarily of a wide variety of species of polycyclic aromatic hydrocarbons (PAH) to which carcinogenicity is attributed.

(a) These PAH include non-volatile N-nitrosamines, aromatic amines (regarded as being the etiologic agents in bladder cancer), isoprenoids, pyrenes, benzopyrenes, chrysenes, anthracenes, fluoranthenes, carcinogenic aza-arenes such as the acridines and carbazoles, and the mutagenic aza-arenes such as the quinolines and phenanthridines.

(b) In addition, the "tar" contains simple and complex phenols, cresols and naphthols, alkanes and alkenes, benzenes and naphthalenes, carboxylic acids, and metallic ions, as well as

radioactive compounds such as potassium-40, lead-210, polonium-210 and radium-226.

(c) The particulate phase also contains agricultural chemicals and additives as flavoring agents and humectants.

Toxic and Carcinogenic Agents

Compounds in cigarette smoke have been classified by an expert panel into:

1. Those judged most likely to contribute to the health hazards of smoking.

(a) Carbon monoxide (gas phase).

(b) Nicotine and "tar" (particulate phase).

2. Those judged as probable contributors to the health hazards of smoking.

(a) Gas phase: acrolein, hydrocyanic acid, nitric oxide and nitrogen dioxide.

(b) Particulate phase: cresols and phenol.

3. Those judged as suspected contributors to the health hazards of smoking.

(a) Gas phase: acetaldehyde, acetone, acetonitrile, acrylonitrile, ammonia, benzene, 2-3 butadione, carbon dioxide, crotononitrile, ethylamine, formaldehyde, hydrogen sulfide, methacrolein, methyl alcohol, and methylamine.

(b) Particulate phase: butylamine, dimethylamine, DDT, endrin, furfural, hydroquinone, nickel compounds, pyridine.

These compounds have been so designated not only because of their harmful actions but also because of their concentrations in tobacco smoke. Although other constituents are considered toxic, they are not present in concentrations deemed a health hazard.

A number of tumor initiators, co-carcinogens, and organ-specific carcinogens have been isolated and identified. The majority of co-carcinogens remain to be identified. The increased risk cigarette smokers have for cancer of the esophagus, kidney, and urinary bladder suggests the possibility that cigarette smoke contains unidentified organ-specific carcinogens besides the known trace amounts of carcinogenic aromatic and N-nitrosamines.

Physiological Response to Cigarette Smoke

1. The smoking of a cigarette seems to satisfy a smoker's physiological and psychological needs, and it is generally accepted that nicotine is the principal constituent responsible for cigarette smokers' pharmacologic responses.

2. Nicotine causes the release of catecholamines, epinephrine and norepinephrine. Several physiologic responses are attributed to nicotine and/or catecholamines such as increased heart rate and blood

pressure, cardiac output, stroke volume, velocity of contraction, myocardial contractile force, oxygen consumption, coronary blood flow and arrythmias, increased mobilization and utilization of free fatty acids, hyperglycemic effects, and a decreased patellar reflex response.

3. Considerable evidence exists, although it is not uniformly accepted, that smoking patterns of chronic smokers are to a large degree dependent on the nicotine content of the cigarette and dependent on what the nicotine delivery would be when measured by the standard methodology. Smoking patterns are dependent, to varying degrees, on the type of cigarette smoked, the number of cigarettes smoked, the length of the cigarette burned, the number of puffs, and the depth and length of inhalation.

Reduction in Toxic Activity of Cigarette Smoke

1. At the present time, selective filtration of carbon monoxide has not proven feasible.

2. Charcoal filtration has proven successful in the removal of certain ciliatoxic substances from the gas phase of cigarette smoke.

3. Selected types of cellulose acetate filter tips selectively remove volatile phenols.

4. Cigarette fillers low in wax-layer components deliver smoke reduced in catechols, but there is a question as to whether selective reduction in cathechols leads to a significant reduction of the tumorigenic potential of cigarette smoke.

5. Lowering nitrate content of tobacco reduces volatile N-nitrosamines in tobacco smoke, but it has not been shown that a reduction of this compound will lead to a significant reduction in the tumorigenic potential of the smoke.

6. Experimentally, a dose-response gradient is demonstrable for "tar" application or smoke inhalation and tumor yield. A number of technical approaches, including modification of the filler, has reduced the "tar" content of smoke.

7. Similar technical approaches have reduced the nicotine content of tobacco smoke.

8. There is a possibility that nonvolatile N-nitrosamines can be reduced by addition of specific bacteria during the processing of tobacco. Selective filtration is not feasible for their removal.

9. A number of methods have led to reduction of "tar" and of toxic and tumorigenic agents in the smoke of cigarettes. Several approaches have led to the reduction of the ciliotoxicity and to selective reduction of the carcinogenicity and tumor-promoting activity of the smoke of experimental cigarettes. Many of these methods have already been incorporated in today's modified, blended U.S. cigarette.

Behavioral Aspects of Smoking

Because of the research over the past 15 years, much is now known about the health dangers of smoking. But research into reasons why the habit is so widespread and difficult to break is still in its infancy; little is known for certain, and questions far outnumber answers.

This part of the report summarizes current understanding of the biological, behavioral, and psychosocial aspects of the cigarette smoking habit and the dependence process associated with smoking. It is no exaggeration to say that smoking is the prototypical substance-abuse dependency and that improved knowledge of this process holds great promise for prevention of risk. Establishment and maintenance of the smoking habit are, obviously, prerequisite to the risk, and cessation of smoking can eliminate or greatly reduce the health threat.

Among the findings, tentative conclusions, and areas for research presented in this section are the following:

1. Nicotine, the most powerful pharmacological agent in cigarette smoke, has been proposed as the primary incentive in smoking and may be instrumental in the establishment of the smoking habit. The proposition that heavy smokers adjust their plasma nicotine levels is compatible with the observation that regular smokers commonly consume about 20 to 30 cigarettes during the smoking day (approximately one every 30 to 40 minutes) and that the biological half-life of nicotine in humans is approximately 20 to 30 minutes.

2. Recent research suggests that specific central nervous system receptor sites for nicotine can be blocked in a fashion analagous to the opiate antagonists. This phenomenon has implications for understanding the effect of nicotine on the body as well as in helping former smokers to maintain abstinence.

3. By far the most common, and clinically the most important, symptom to appear following withdrawal from tobacco is craving for tobacco. The importance of the tobacco-withdrawal syndrome is its provocative role in relapse among abstinent smokers. Abrupt and total withdrawal from tobacco is associated with a withdrawal syndrome that subsides more quickly and is no worse than that seen in partial abstinence. A partially-abstinent smoker is in a chronic state of withdrawal that typically leads to relapse and a return to baseline rates of smoking.

4. There is fragmentary evidence suggesting that the abstinence syndrome is more severe in women than in men, and it seems likely that this is at least partly responsible for lower rates of successful cessation among women.

5. Little is known about the millions of smokers who have quit on their own. It has been estimated that 95 percent of the 29 million smokers who have quit since 1964 have done so on their own.

6. Survey data show that only one-third or less of smokers motivated to quit are interested in formal programs, and only a small minority of

those who do express an interest actually attend programs when offered. It thus appears that available objective outcome data may be based on a small minority sample of smokers at large.

7. Objective data are lacking on most of the smokers who have been willing to attend formal programs. Public service clinics continue, but lack of objective outcome data precludes the evaluation of their efficacy. Similarly, proprietary programs remain virtually unmonitored and unevaluated in an objective fashion. Controlled research has yet to produce a clearly superior intervention strategy. However, rapidly accumulating and improving data now suggest that multicomponent interventions offered by intervention teams with practical knowledge regarding the smoking problem are the most encouraging.

8. Too few carefully designed and implemented longitudinal studies exist in the area of smoking in children and adolescents to allow for true evaluation of the effectiveness of many past programs developed for them.

9. Inferences about the evolution of smoking suggest that by the end of the ninth grade very few adolescents are addictive smokers; the critical level of the onset of addictive smoking appears to be in high school. Therefore, the true impact of any deterrence-of-smoking program with adolescents may not even be measurable until after the adolescent has entered high school. This problem is not unlike the recidivism encountered in virtually all smoking cessation programs.

10. Too many programs for youth have focused on information about smoking or fear of serious disease due to smoking. Adolescents are present-oriented and appear to be less influenced by messages concerning smoking that focus exclusively on long-term dangers.

11. A focus on research into prevention of the onset of addictive smoking appears to be a reasonable parallel course to follow along with efforts at control and cessation.

12. A promising new approach may be in the "inoculation" of adolescents against various pressures to smoke which apparently override their knowledge about the dangers of smoking. The approach involves strategies to resist peer pressure, emphasis on understanding of how advertising and mass media work to influence smoking, and provision of information on ways to resist the models of parents, siblings, and older students who smoke. Also included is a focus on the immediate physiological effects of smoking rather than on long-term effects.

Education and Prevention

Research strongly indicates that educators and health care providers teach youth about smoking and health as much by example as through formal instruction. But, despite a proliferation of a wide variety of educational programs aimed at youth and adults, it is not known which methods are most effective in preventing the start of smoking or in

promoting cessation. Summarized below are some of the research findings, program and experimental approaches, and needs in the areas of smoking education and prevention discussed in this part of the report.

1. Most educational programs are based on what seems reasonable rather than on sound theoretical models. It is logical to assume, for example, that young people who know about the harmful effects of cigarette smoking on health will resist smoking. Thus, many programs are based on knowledge dissemination and a health threat. However, we know that 94 percent of teenagers say that smoking is harmful to health and 90 percent of teenage smokers are aware of the health threat.

2. The trend in adult education programs is toward emphasis on personal responsibility for individual health and adoption of a health-promoting lifestyle.

3. Researchers find that "significant adults"—physicians, nurses, dentists, other health professionals, coaches, and parents—are powerful influences on teenage smoking. A nationwide survey of teenagers, for example, indicated that 72 percent of the nonsmokers identified physicians as the one group that could influence them not to start smoking; 43 percent of the smokers felt that the physician's advice would influence their decision to stop smoking.

4. Health professionals as a group have preceded the general public in improving their smoking habits; they have stopped smoking, moved to less hazardous forms of tobacco, or reduced the amount smoked.

5. Several studies of methodologies used in smoking education reported mixed results, with no method clearly predominating.

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PART I

THE HEALTH CONSEQUENCES OF SMOKING

2. MORTALITY.

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Introduction

Cigarette smoking is the single most important environmental factor contributing to premature mortality in the United States. This preventable, premature mortality is due to increased death rates among cigarette smokers from several diseases, but primarily from ischemic heart disease, cancers of the respiratory tract, and the chronic obstructive pulmonary diseases, emphysema, and chronic bronchitis.

The world's literature on smoking and health at present consists of more than 30,000 published articles from thousands of studies conducted in every major country of the world. These data are housed in the Technical Information Center of the Office on Smoking and Health in the Department of Health, Education, and Welfare.

During the past 30 years, there have been eight large prospective epidemiological studies conducted that were specifically designed to delineate the relationship between tobacco smoking and the development of disease. Several of these studies were in progress at the time of the first report on smoking and health by the U.S. Government (*37*). Within the past 2 years, reports on long-term follow-up have been published from four of these studies, which are still in progress (*9, 19, 21, 33*). The longest follow-up comes from the study of British physicians, from which 20-year data have been published (*9*). The largest study is the American Cancer Society study of men and women in 25 States that enrolled more than one million subjects and is easily one of the largest studies of all time. Twelve-year follow-up data from this population have been published (*19*). A representative population study from Sweden includes data on men and women (*2*).

The relationship between smoking and overall mortality has been reviewed by the Department of Health, Education, and Welfare several times during the past 15 years. A report of the Advisory Committee to the Surgeon General of the Public Health Service was first published in 1964 (*37*). The subject was again reviewed in 1967, 1968, and 1978 in *The Health Consequences of Smoking* (*34, 35, 36*).

The effect of cigarette smoking on overall mortality as reported in the eight major prospective epidemiological studies is summarized in this chapter. Recently published data from these studies have resulted in numerous refinements in our understanding of smoking and overall mortality. The major conclusions drawn in 1964 still stand, but they are reinforced by the weight of evidence accumulated from these and other sources over the past 15 years. Conclusions regarding smoking and overall mortality reported in previous reports will not be presented here. The summary appearing at the end of this chapter is a synthesis of all that is currently known about smoking and overall mortality. It includes data from previous reports as well as current conclusions based on the most recently published data.

The Measures of Mortality

Overall mortality is a measure of the cumulative or total effect of a disease-causing agent on the health of a population. Overall mortality rates are particularly useful in determining the effect of agents that influence multiple organ systems and result in increased death rates from several diseases. Overall mortality is the best way to measure the sum of the risk due to cigarette smoking-related diseases. Smoking directly exposes multiple sites in the respiratory tract to the chemical constituents of tobacco smoke. This direct effect is most likely responsible for the increased mortality smokers experience from cancer of the lung, larynx, oral cavity, and esophagus, as well as the chronic obstructive diseases of the lung, emphysema, and chronic bronchitis. The more soluble compounds are absorbed into the blood stream where, unchanged or in some cases as toxic metabolites of parent compounds, they act upon susceptible tissues not directly exposed to cigarette smoke. This effect is most likely responsible for the increased mortality smokers experience from ischemic heart disease, aortic aneurysm, and cancers of the urinary bladder and pancreas. Because of these complexities, only overall mortality rates can present an accurate statement of the impact of smoking on the health of the population.

Although overall mortality is frequently used by epidemiologists and statisticians, it has little immediate application to the practice of many physicians, dentists, nurses, or other health professionals whose orientation is primarily clinical and who deal more with specific diseases and disease-specific mortality rates. Usually, when a disease-causing agent results in increased mortality for only one disease, there may be a sharp increase in the death rate for that specific disease, but there will be very little change in the overall mortality rate for the population. By contrast, cigarette smoking increases the death rates for several diseases. As a result, overall mortality rates are increased more than the disease-specific death rates for several of the diseases caused by cigarette smoking.

Overall mortality can be expressed in several ways. The most commonly used terms are listed below with a brief discussion of their significance.

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

2. Differences in Mortality Rates: Obtained by subtracting from the death rate for smokers, the death rate of a comparable group of nonsmokers. This measure reflects the added probability of death in a

TABLE 1.—Mortality ratios, differences in mortality rates and excess deaths by age as derived from two studies

	Age				
	35–44	45–54	55–64	65–74	75–84
U.S. Veterans Study (males)					
Total deaths	383	366	13,840	17,550	1,932
Death rates: nonsmokers	127	264	1,056	2,411	6,214
Death rates: cigarette smokers	232	728	1,819	4,032	8,417
Mortality ratio	1.83	2.76	1.72	1.67	1.36
Difference in mortality rates	105	464	763	1,621	2,257
Excess deaths as a percentage of total	33	43	21	17	8
25 State Study (males)					
Total deaths	631	5,297	8,427	8,125	3,968
Death rates: nonsmokers	210	406	1,202	3,168	7,863
Death rates: cigarette smoker	397	925	2,202	4,788	9,674
Mortality ratio	1.89	2.28	1.83	1.51	1.23
Difference in mortality rates	187	519	1,000	1,620	1,811
Excess deaths as a percentage of total	33	38	25	13	4

SOURCE: Hammond, E.C. (*17*), Kahn, H.A. (*26*).

1-year period for the smoker over that for the nonsmoker. As such, it is a measure of *personal health significance*, a means for the individual to estimate the added risk to which he or she is exposed.

3. Excess Deaths: Obtained by subtracting from the number of deaths occurring in a group of smokers, the number of deaths that would have occurred if that group of smokers had experienced the same mortality rates as a comparable group of nonsmokers. This measure is an indicator of the *public health significance* of the differences, since it measures the number of people affected and, therefore, the magnitude of the problem for society as a whole.

4. Life Expectancy: A concept that is easier to understand than to calculate. At a given age, it represents the average number of years one might be expected to live.

Table 1 illustrates the first three measures for five age groups of men from the U.S. Veterans Study and the American Cancer Society Study of Men in 25 States. Table 2 illustrates the effect of cigarette smoking on life expectancy using data from the 25-State Study and the U.S. Veterans Study. When compared to non-smokers, an average young male smoker (30 to 40 years of age) who smokes more than 40 cigarettes per day loses an estimated 8 years of life.

TABLE 2.—Estimated years of life expectancy (LE) for males at various ages by amount smoked, as derived from two studies

Cigarettes smoked per day	Age							
	30		40		50		60	
	LE	Years lost	LE	Years lost	LE	Years lost	LE	Years lost
25 State Study								
Nonsmokers	43.9	0	34.5	0	25.6	0	17.6	0
1–9	39.3	4.6	30.2	4.3	21.8	3.8	14.5	3.1
10–19	38.4	5.5	29.3	5.2	21.0	4.6	14.1	3.5
20–39	37.8	6.1	28.7	5.8	20.5	5.1	13.7	3.9
40+	35.8	8.1	26.9	7.6	19.3	6.3	13.2	4.4
	35		40		50		60	
U.S. Veterans Study								
Nonsmokers	43.5	0	38.7	0	29.4	0	20.8	0
1–10	41.0	2.5	36.3	2.4	27.5	1.9	19.0	1.8
10–20	38.7	4.8	34.1	4.6	25.2	4.2	17.2	3.6
21–39	36.7	6.8	32.0	6.7	23.4	6.0	15.8	5.0
40+	34.8	8.7	29.9	8.8	21.6	7.8	14.4	6.4

SOURCE: Hammond, E.C. (*17*), Rogot, E. (*31*).

The Major Prospective Epidemiological Studies

Below are brief outlines of the eight important prospective epidemiological studies and their results. Taken together, the eight studies encompass more than 16 million person-years of experience and over 300,000 deaths. The data are presented in Table 3. Numbers in the table have been rounded, for ease of presentation.

The British Doctors Study (*4*)

In 1951, the British Medical Association forwarded to all British doctors a questionnaire about their smoking habits. A total of 34,400 men and 6,207 women responded. With few exceptions, all men who replied in 1951 have been followed for 20 years. Further inquiries about changes in tobacco use and some additional demographic characteristics of the men were made in 1957, 1966, and 1972. More than 10,000 deaths have occurred in this population during the past 20 years.

The American Cancer Society 25-State Study (*17*)

In late 1959 and early 1960, the American Cancer Society enrolled 1,078,894 men and women in a prospective study. All segments of the population were included except groups that could not be traced easily. A lengthy initial questionnaire was administered that contained