Illustration

List of Tables

Chapter 9

CANCER MORBIDITY AND MORTALITY

Cancer has been the second ranking cause of death in the United States since 1937. Reviewing the mortality statistics of those parts of the United States which began relatively accurate reporting in 1900, (District of Columbia and 10 states—the so-called Death Registration Area of 1900) it can be seen that the number of cancer deaths per year has increased markedly (Figure 1). After subtracting the part of the increase due to growth of the population and the part due to increase in life expectancy or aging of the population, there is still a residual increase of significant proportions. While a part of this is undoubtedly due to improvement in diagnosis, most observers agree that a true increase in the cancer death rate has occurred during this time.

As general background information, it is useful to review the pattern of cancer risks found in the population of the United States as compared with the patterns in other countries. Segi has prepared systematic international compilations of cancer mortality (317). These show that the United States occupies an intermediate position in comparisons of death rates for all sites combined: the age-adjusted rates for U.S. males and females are lower than those in Austria and higher than in Norway and Japan (Figure 2). The point to be stressed, however, is not the rank order of countries according to over-all cancer mortality, but the differences in ranking for individual sites (Figures 3A and 3B). Mortality statistics, cancer register data, and collected series of pathological specimens are in general agreement in identifying individual countries as having their own characteristic site patterns of risk (146). Some of the more striking features in the United States are very low risks for esophagus and stomach and moderately high rates for urinary bladder; lung cancer mortality for males, while below the rates in England and Finland, is well above those in Canada, Norway and Japan.

Sources of Information

Information on morbidity and mortality from cancer in the United States comes from three principal sources: mortality statistics prepared by the National Vital Statistics Division of the U.S. Public Health Service, the large central registries receiving reports on diagnosed cases in Connecticut (136) upstate New York (112) and California (37), and the morbidity surveys conducted in ten metropolitan areas in 1937–39 and 1947–48 (91) and in Iowa in 1950 (148). Each body of material has its virtues and weaknesses. Mortality statistics report on the national experience and cover longer time spans than the specialized sources, but the diagnostic information in the death certifications is less reliable and complete. Recent studies of medical certifications have demonstrated that the quality of information for most

MORTALITY FROM CANCER (All sites), U.S. DEATH REGISTRATION AREA [1] OF 1900, 1900-1960

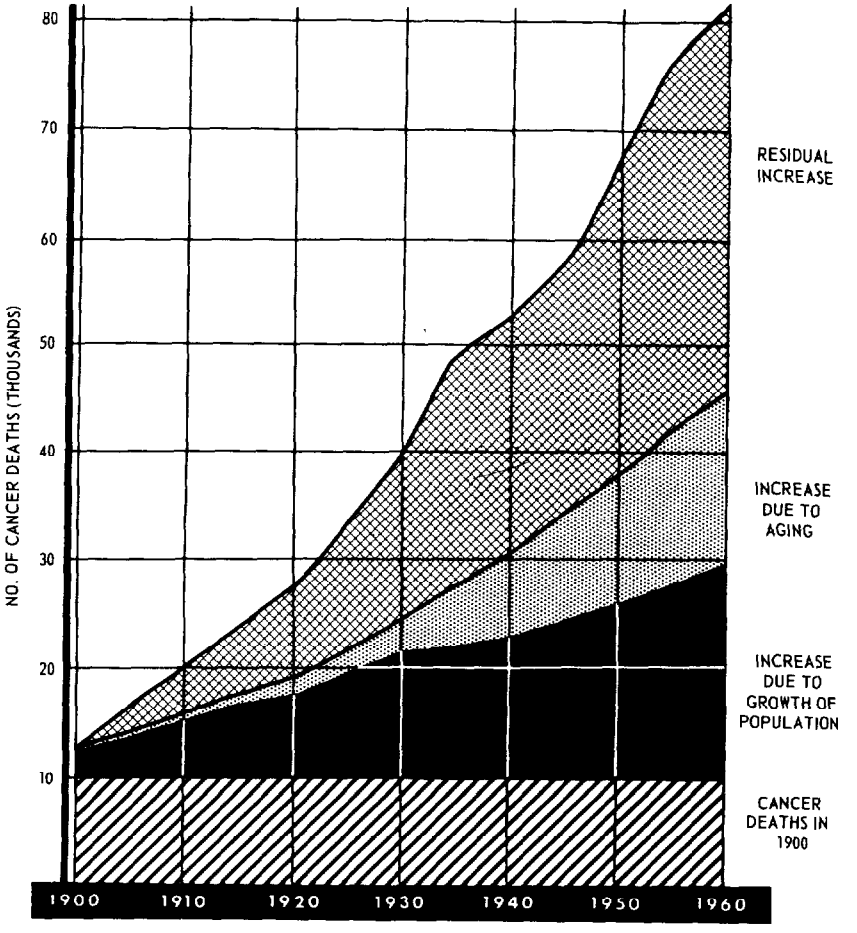

FIGURE 1.

Includes Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, Michigan, Indiana, District of Columbia.

Sources: a. United States Census of Population: 1940, 1950, 1960.
b. Vital Statistics of the United States, Part I, 1940; Vol. III, 1950; Vol. II, Part B, 1960.
c. Gover, Mary. Cancer Mortality in the United States, Part I, Public Health Bulletin 248, 1939.

cancer sites can be regarded as good (91, 247), so that the problems in interpretation are less formidable than those arising in studies of cardiovascular disease.

Completeness of reporting to the major registries is satisfactory and the accuracy of diagnostic information is excellent, but the registers cover only a limited number of areas. Fortunately, the registers in Connecticut

AGE-ADJUSTED MORTALITY RATES FOR CANCER - ALL SITES, IN 17 COUNTRIES 1958-1959. [1]

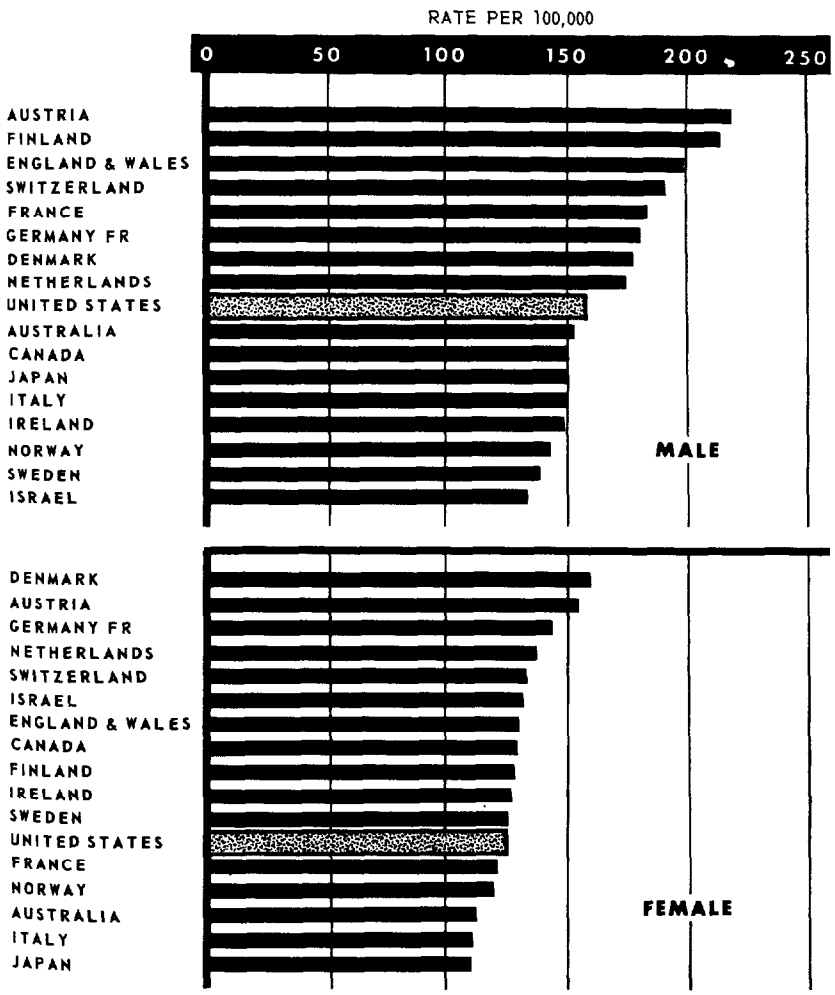

FIGURE 2.

U.S. data age-adjusted to total population of the continental United States, 1950.

Source: Calculated from Segi, M., and Kurihara, M. (317).

and New York have been in operation long enough to provide reliable data on incidence trends over the past two decades. The morbidity surveys for 1947–48 produced a comprehensive report on cancer incidence in large cities with very good medical care facilities, but this information has not been updated by resurveys.

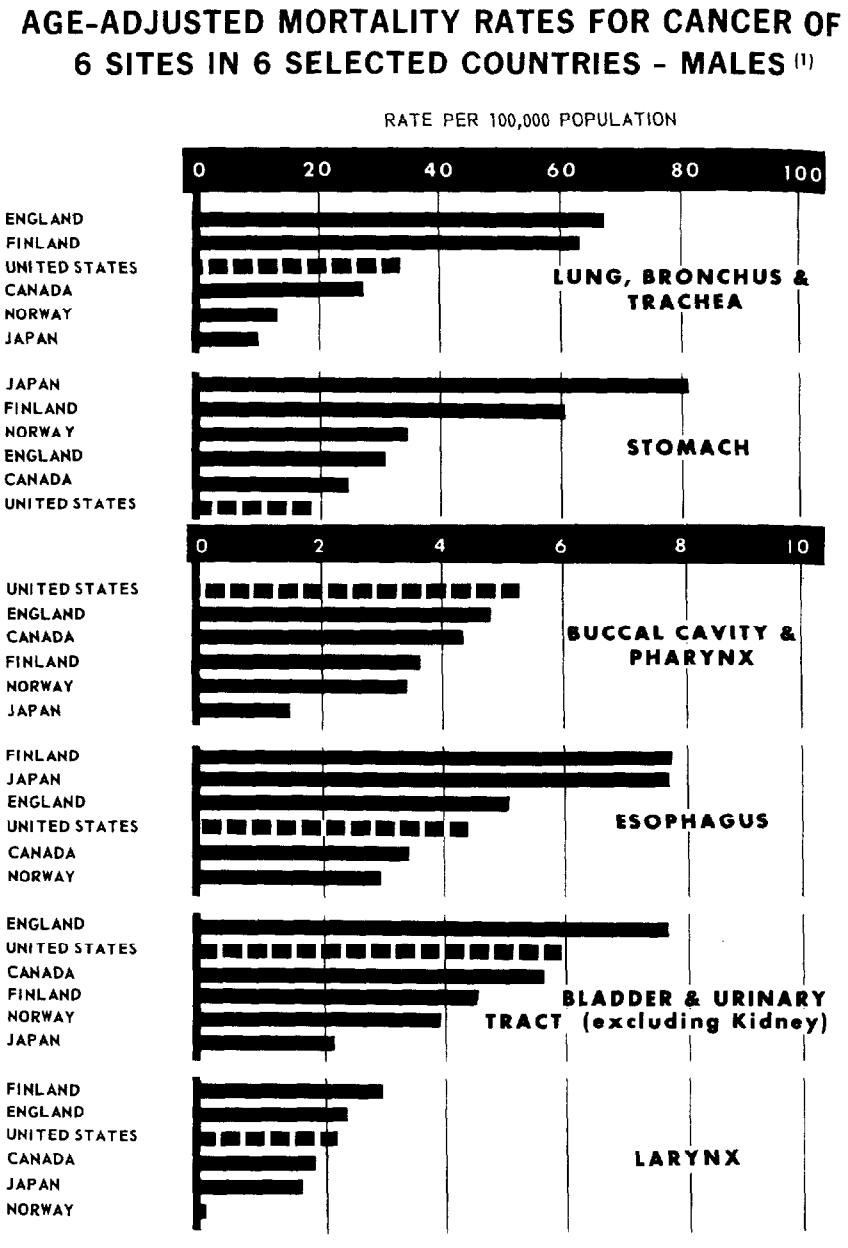

FIGURE 3A.

U.S. data age-adjusted to the total population of the continental United States, 1950.
Source: Calculated from Segi, M., and Kurihara, M. (317).

The deficiencies in any single set of data should not be overstressed. Comparisons of the various sources indicate good internal consistency among them and they usually lead to the same inferences on patterns of risk for

AGE-ADJUSTED MORTALITY RATES FOR CANCER OF 6 SITES IN 6 SELECTED COUNTRIES - FEMALES [1]

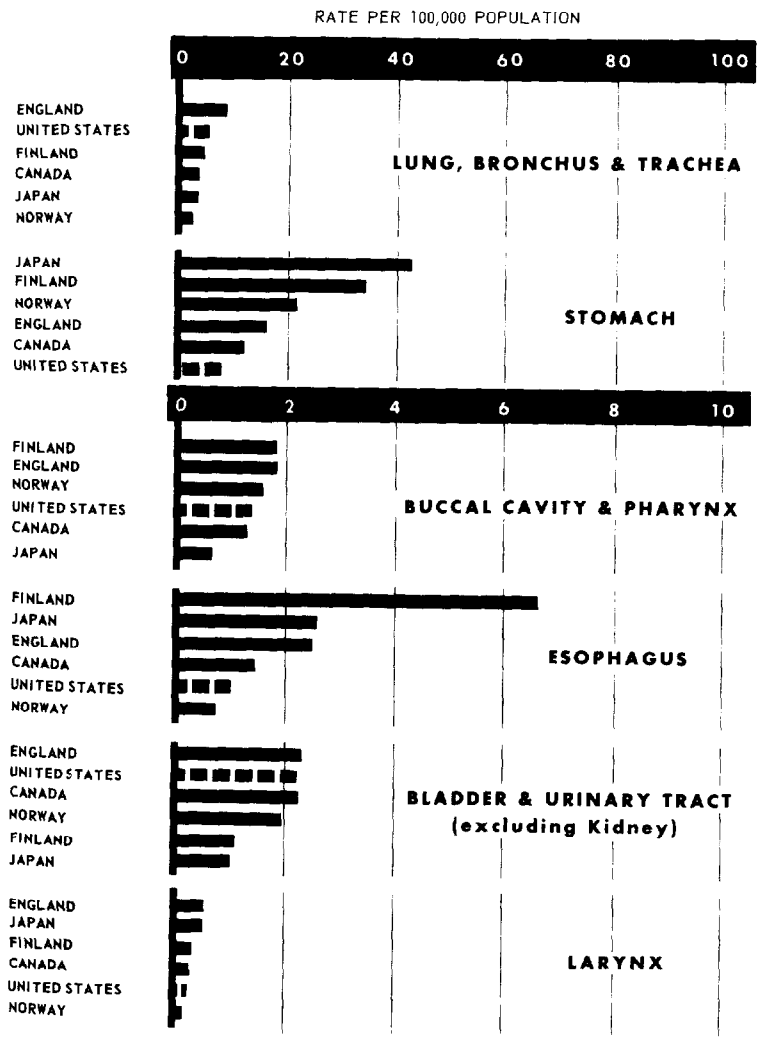

FIGURE 3B.

U.S. data age-adjusted to the total population of the continental United States 1950.

Source: Calculated from Segi, M., and Kurihara, M. (317).

individual sites, particularly those for which the five-year survival rates are very low. Figure 4, which contrasts recent mortality and incidence rates, demonstrates that these rates differ markedly only for sites with more favorable prognosis—oral cavity, prostate, and urinary bladder. These differences are compatible with existing information on the survival experience of cancer patients.

COMPARISON OF AGE-ADJUSTED MORTALITY RATES BY SEX IN THE UNITED STATES 1959-1961 WITH INCIDENCE RATES FROM STATE REGISTRIES - UPPER NEW YORK STATE 1958-1960 AND CONNECTICUT 1959.

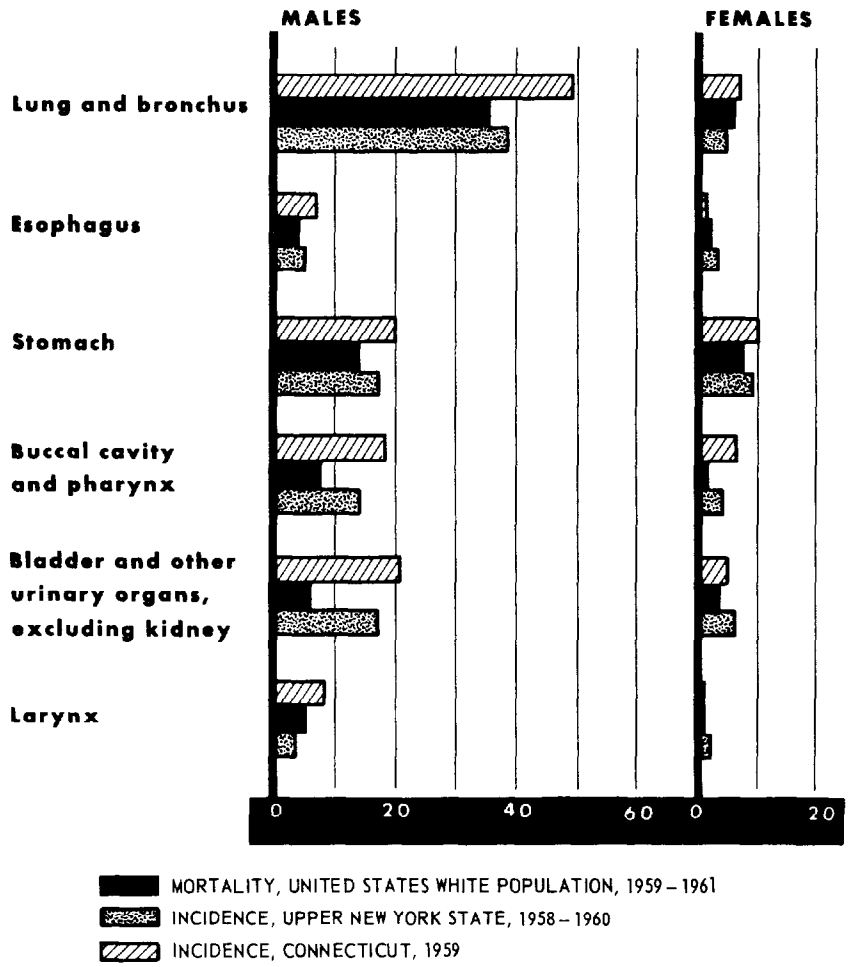

FIGURE 4.

Sources: Vital Statistics of the United States, annual volumes; Ferber, B. et al (112). Eisenberg, H., personal communication to the Surgeon General's Advisory Committee on Smoking and Health.

The next sections describe some aspects of incidence or mortality for eight sites—lung and bronchus, larynx, oral cavity, esophagus, urinary bladder, kidney, stomach and prostate. Of these, six were selected for spe-

cial consideration because they are the ones most often reported by the prospective studies to have the highest mortality ratios of tobacco-users to non-users, and stomach was included because the trend in cancer of this organ in recent years has been in such marked contrast to that for cancer of the lung and bronchus.

Sex Ratio

The male-female ratios of age-adjusted death rates (U.S., 1959–61) (252) from cancer for the six sites common to both sexes are given below:

	Male/Female Ratio Whites	*Male/Female Ratio Nonwhites*
Larynx	10.8	7.6
Lung and bronchus	6.7	6.2
Oral cavity	3.8	3.3
Esophagus	4.1	4.2
Stomach	2.0	2.3
Urinary bladder	1.3	1.6

The ratios of male/female death rates vary with site: ranging from about 10 to 1 for larynx to much less than 2 to 1 for urinary bladder, the findings for white and nonwhite populations being in substantial accord. The male-female ratios for five of the six sites have remained quite stable over the past 30 years, lung cancer providing the important exception. The lung cancer sex ratio was 1.5 to 1 in 1930 and has steadily increased during the intervening period to the current value of over 6 to 1. Mortality, register and survey data yield consistent information on sex ratios, and material from the latter sources need not be reproduced here.

Geographic Variation

Cancers of the oral cavity, larynx, lung and bronchus, prostate, and urinary bladder do not exhibit any consistent marked regional departures from the over-all U.S. incidence and mortality experience (91, 130). Cancer of the esophagus is higher in the Northeast and North Central regions, and gastric cancer is encountered less frequently in the South than in other parts of the country. Within regions, some cities are known to display exceptional incidence of certain types of cancer (91).

Urban-Rural Gradients

The excess risk for residents of urban areas is most pronounced for cancer of the lung and bronchus, oral cavity, and esophagus. This urban excess is not characteristic of the data for stomach, prostate, or bladder (208).

Income Class

Information on income class gradients in cancer risks by site was secured in the morbidity surveys of ten U.S. metropolitan areas in 1947–48 (91).

According to this source, incidence was inversely related to income class for five sites under review—oral cavity, esophagus, stomach, larynx, lung. The rates for males in the lowest income class for esophagus and lung were about double those for high income males; the range for the remaining sites was not quite so pronounced, the excess in low income risks being on the order of 60–80 percent. For one site within the oral cavity, salivary glands, no relationship was found between incidence and income class. The inverse gradient by income class, while present, was much weaker among females for esophagus, stomach, and lung. The female risks for cancer of the oral cavity and the larynx were too small to permit meaningful statements on this topic. Incidence of bladder cancer was not related to income class for either males or females.

Occupation

From unpublished tabulations of deaths for 1950 according to occupation and industry prepared by the National Vital Statistics Division of the Public Health Service (252), it is possible to select certain occupations with unusually high mortality for specific sites. One of the more striking results is the liability of bartenders, waiters, and others engaged in the alcoholic beverage trade to oral and esophageal cancers, the mortality ratios being about double those for all males of comparable age. Similar findings have been reported by the Registrar-General of England and Wales (135).

Review of the distribution of lung cancer risks by occupation indicates a large variety of occupational groups in metal working trades, such as molders, boilermakers, plumbers, coppersmiths, sheet metal workers, etc., who are subject to a 70–90 percent excess risk for this site.

One feature which does not come through clearly in the rather crude occupational mortality data is the high risk of bladder cancer among workers exposed to aromatic amines, as established by observations on workers in individual plants (179, 336). The 50 percent excess of bladder cancer mortality of workers in chemical and allied industries, reported in vital statistics, must represent a dilution of higher risks in specific occupations in which the hazards are much greater. This dilution occurs because data from a number of industries and occupations, including many in which no particular bladder cancer hazards are present, are pooled in broad categories.

Ethnic Group

Foreign-born migrants to the United States as a group have age-adjusted death rates for cancer of the esophagus and stomach about twice those recorded for native-born white males and females. Lung cancer mortality is about one-third higher among the foreign-born, again for both sexes. No important differential between native- and foreign-born has been observed for oral cancers (both sexes) or for bladder (males); the rates for bladder cancer are about 30 percent lower for women born abroad than for women born in the United States. Laryngeal cancer has not been systematically studied from this point of view (144).

The several ethnic groups in the United States display their own characteristic patterns of excesses and deficits in risk by site. Men and women born in Ireland have high death rates for oral and esophageal cancers. The Polish-born Americans have pronounced excess mortality for esophageal and gastric cancers for both sexes, and Polish males rank first in lung cancer. The Russian-born, a large proportion of whom are Jews, show high death rates for stomach (both sexes) and a striking excess risk for esophageal cancer among women. The English-born American men and women have above-average lung cancer risks.

Trends

Figure 5 describes the divergent behavior in mortality trends for cancer, all sites, among men and women since 1930. The age-adjusted death rate has been declining slightly in females, but increasing in males; most of the rise for males is obviously attributable to the sustained upturn in lung cancer certifications.

The succeeding logarithmic graph (Figure 6) portrays trends in mortality among whites for individual sites; nonwhites have been excluded because the comparability of data over time for this group would be affected more seriously by recent improvements in quality of death certifications. Lung cancer mortality among males has risen at a fairly constant rate since 1930; for females the trend has also been consistently upward, but at a much slower pace. This form of cancer was responsible for the deaths of approximately 5,700 women and 33,200 men in the United States in 1961. As recently as 1955, the corresponding totals were 4,100 women and 22,700 men (252). The register and survey data also have reported a marked rise in lung cancer incidence. No other cancer site has exhibited in recent history a rate of increase, absolute or relative, approaching that recorded for lung cancer in males.

Inspection of age-adjusted mortality rates for oral cavity, esophagus, larynx, prostate, and urinary bladder cancers pinpoints no dramatic shift in risk. The rates for stomach cancer, however, have been declining steadily. This has led some observers to conjecture that the rise in lung cancer and the decline in stomach cancer may represent two aspects of the same phenomenon, a progressive transfer of deaths to lung cancer which might formerly have been certified as stomach cancer. Detailed examination of the data on possible compensatory effects by country, sex, age and other variables conclusively rules out diagnostic artifacts of this type as a possible explanation.

The Connecticut and New York State registers (112, 136) and the ten-city surveys (91) confirm the decline in gastric cancer and the absence of important changes over time for oral cavity, esophagus, urinary bladder, and kidney, and show a small increase for larynx. The registers also indicate a small rise in incidence of prostatic carcinoma; the age-adjusted rate in upstate New York increased from 21.4 in 1941–43 to 24.9 in 1958–60, and the Connecticut experience revealed a similar displacement. A possible reason for this increase in case reports of prostatic cancer to registers may be found in more careful examination by pathologists of prostates removed

TRENDS IN AGE-ADJUSTED MORTALITY RATES FOR CANCER BY SEX - ALL SITES AND RESPIRATORY SYSTEM IN THE UNITED STATES, 1930-1960. [1]

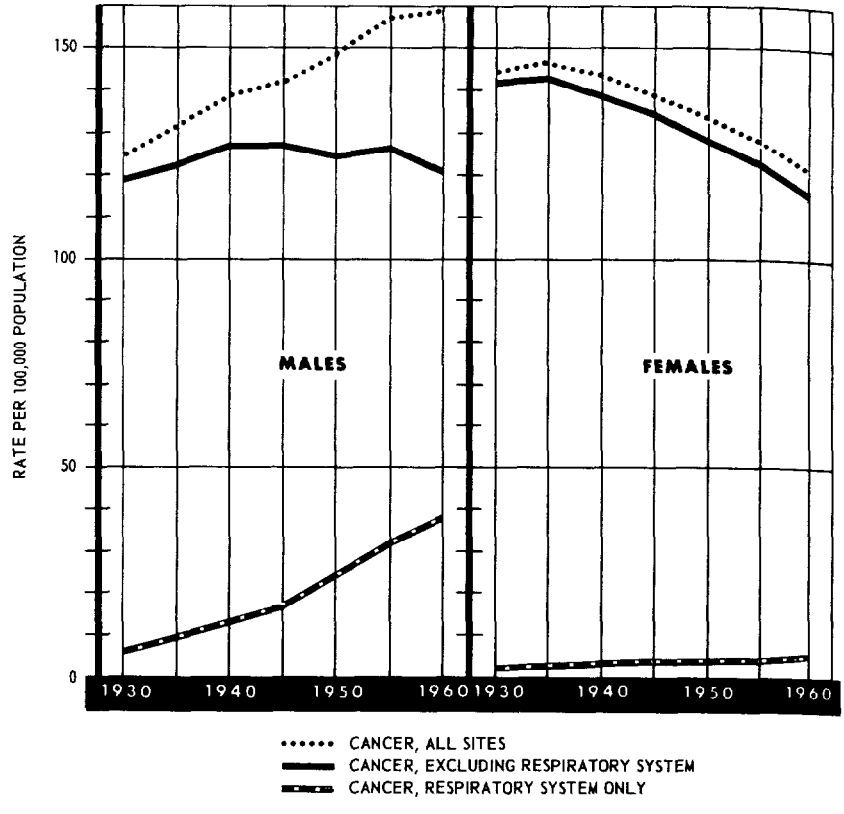

FIGURE 5.

Age-adjusted to the total population of the continental United States, 1950.

Source: Vital Statistics of the United States, annual volumes.

surgically, which would result in discovery and reporting of more asymptomatic prostatic carcinomas. The mortality data relate to clinically active prostatic carcinomas and in this instance probably give a more accurate assessment of changes over time than the registry data.

AGE-SPECIFIC MORTALITY FROM LUNG CANCER

The schedules of age-specific lung cancer mortality rates for males studied in five successive time periods from 1914 to 1960 are shown in Figure 7 (dotted lines). It can be seen that the rate rises to a maximum at age 70 and then declines gradually thereafter. Incidence data from cancer registers provide a close parallel (112).

TRENDS IN AGE-ADJUSTED MORTALITY RATES FOR SELECTED CANCER SITES BY SEX IN THE UNITED STATES, 1930-1960. [1]

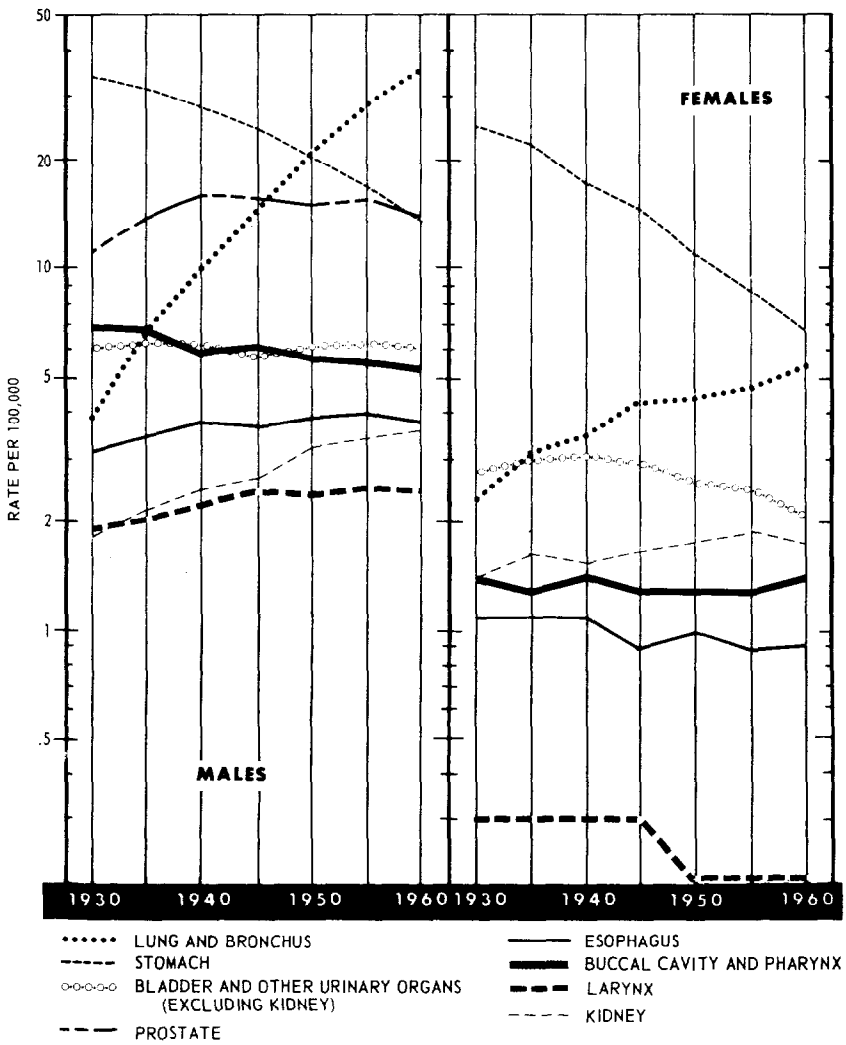

FIGURE 6.

Data are for the white population, age-adjusted to the total population of the continental United States, 1950.

Sources: Gordon T., et al. (130); and unpublished calculations of the Biometry Branch, National Cancer Institute, U.S. Public Health Service.

However, when any separate cohort (a group of persons born during the same ten-year period) is scrutinized over successive decades, the seeming downturn of mortality rates after age 70 can be seen to be an artifact due

AGE-ADJUSTED MORTALITY RATES FOR CANCER OF THE LUNG AND BRONCHUS BY BIRTH COHORT AND AGE AT DEATH FOR MALES, UNITED STATES 1914, 1930-32 , 1939-41, 1949-50, 1959-61. (1)

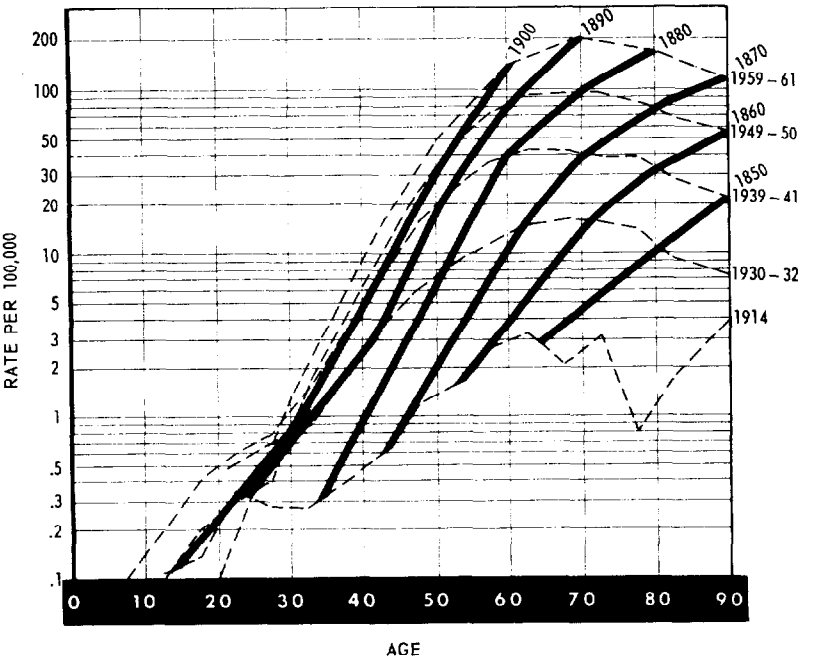

FIGURE 7.

Data are for the white population.

Sources: Dorn, H. F., and Cutler, S. J. (91).

Unpublished calculations of the Biometry Branch, National Cancer Institute, U.S. Public Health Service.

to the admixture of cohorts with differing mortality experiences. When the points representing mortality rates among members of the same cohort group are connected, from each dotted-line curve to the next, the new curve (each of the bold lines) represents the mortality rates over time for the members of a cohort. Thus, to cite the cohort born around 1880 as an example, the bold-line curve shows the mortality rates of the cohort in 1914 when its members were about 34 years old, in 1930–32 when they were about 51 years old, in 1939–41 when they were about 60 years old, in 1949–50 when they were about 70 years old, and in 1959–61 when they were about 80 years old.

The new series of curves, representing the mortality experience of the individual cohorts, reveal two important facts: (a) Within each cohort, lung cancer mortality increases unabated to the end of the life span; and (b) successively younger cohorts of males are at higher risks throughout life

AGE-ADJUSTED MORTALITY RATES FOR CANCER OF THE LUNG AND BRONCHUS BY BIRTH COHORT AND AGE AT DEATH FOR FEMALES, UNITED STATES 1914, 1930-32, 1939-41, 1949-50, 1959-61. (1)

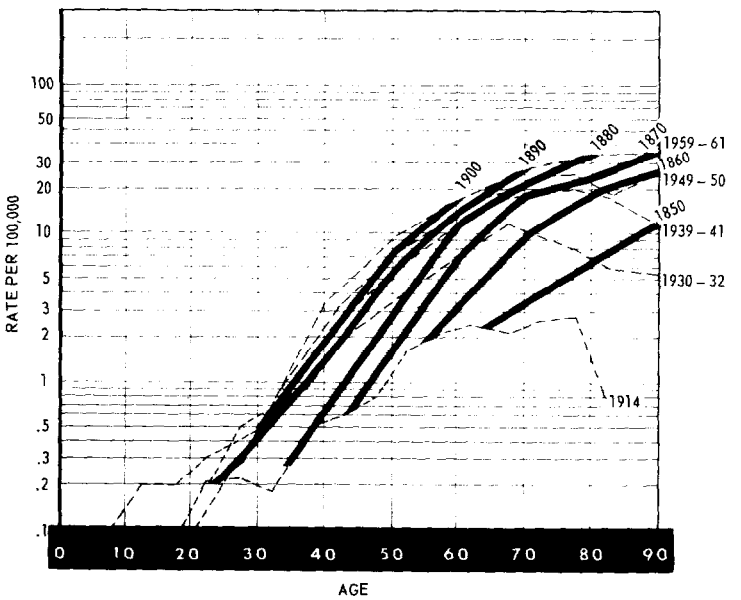

FIGURE 8.

Sources: Dorn, H. F., and Cutler, S. J. (91).

Unpublished calculations of the Biometry Branch, National Cancer Institute, U.S. Public Health Service.

than their predecessors. The increasing steepness of the slope of the cohort mortality curves, beginning with the 1850 cohort and examining the cohort curves from right to left, shows that the rise in lung cancer mortality is much more rapid in the recent cohorts. The pattern would suggest that the effects noted may be attributable to differences in exposure to one or more factors or to a progressive change in population composition among the several cohorts.

For women, incidence and mortality increase up to the older ages, when the rates fluctuate irregularly (Figure 8). A cohort approach to the female experience reveals only small displacements in rates between successive cohorts, the effects being smaller than those noted for males.

EFFECTS OF CHANGES IN LUNG CANCER DIAGNOSIS ON TIME TRENDS

The cause of death is at times difficult to establish accurately from clinical findings alone, and the incidence and mortality rates recorded for lung

cancer vary with the diagnostic criteria adopted (147, 148). A pathologic anatomic diagnosis provides the most reliable evidence for the classification of lung cancer deaths.

Shifts in diagnostic standards or in diagnostic errors must be considered in evaluating the trends in lung cancer mortality shown in tabulations prepared by the offices of vital statistics. In recent years, about two-thirds of the certifications of lung cancer deaths have been based on microscopic examination of tissue from the primary site and the percentage is even higher for deaths under 75 years (146, 247). The proportion of lung cancer certifications in the 1920's and 1930's based on comparable diagnostic evidence is unknown, but the figure was certainly much lower.

Gilliam (128) has attempted to evaluate the possible effects of diagnostic changes on the published lung cancer mortality statistics. He calculated that if two percent of the deaths certified to tuberculosis in 1914 were really due to lung cancer, the observed increase in bronchogenic carcinoma between 1914 and 1950 could be scaled down from 26- to 8-fold for males and from 7-fold to 1.3-fold for females. If 1930 or a later year had been used as the point of departure to estimate the effects of continued misdiagnoses of tuberculosis on this scale, the downward revision in the slope of the lung-cancer rates would have been much smaller. The improved accuracy of lung cancer diagnoses must be conceded, so that the issue remains a quantitative one: what part of the recorded increase can be accounted for by control of diagnostic variation? Retrospective adjustment of vital statistics from past years can yield only rough qualitative judgments (267), and we must rely on the composite evidence from several sources.

The following points have been advanced to support the thesis of a real increase in lung cancer (62):

(a) The rising ratio of male to female deaths

(b) The increasing mortality among successively younger cohorts

(c) The magnitude of the increase in mortality in recent years

To this we would add that the question can be resolved by reference to the contemporary experience of large, population-based cancer registers for which a high percentage of the cases reported have microscopic confirmation. Sufficient time has now elapsed to permit the tumor registries in Connecticut (136) and New York (112) to supply convincing evidence for a true increase in lung cancer. Diagnostic comparability is a far less important consideration in the review of data collected by cancer registries. Between 1947 and 1960 there were no significant advances in diagnostic methods (exfoliative cytology studies of the sputum have been used for diagnostic purposes since 1945). In upstate New York the age-adjusted incidence of lung cancer per 100,000 males rose from 17.8 in 1947 to 41.0 in 1960 and for females from 3.2 to 4.9. These figures imply an average annual rate of increase of about 7 percent for males and 3–3.5 percent for females during this interval.

For earlier years the relative frequency data from necropsy series contribute valuable information. The records of large general hospitals where diagnostic accuracy of lung cancer has been uniform and excellent for many years also support the thesis of a real increase in lung cancer. Institutions such as the University of Minnesota Hospitals (Minneapolis) (350), Presby-

terian Hospital (New York City) (323), and the Massachusetts General Hospital (Boston) (54), now find many more lung cancers than in the past. In the Massachusetts General Hospital, for example, only 17 cases of bronchogenic carcinoma, 11 males and 6 females, were diagnosed in 5,300 autopsies from 1892 to 1929 (autopsy rate of 33 percent), compared to 172 cases, 140 males and 32 females, in 5,000 autopsies from 1956 to 1961 (autopsy rate of 68 percent). This American experience is consistent with that reported abroad, where virtually all patients dying in certain hospital services have been subjected to autopsy for many years. Steiner (328) summarized several such series and Cornfield et al. (62) returned to the original sources and found the collective evidence to affirm a rise in the percent of lung cancers found at necropsy from 1900 on.

The Copenhagen Tuberculosis Station data, reviewed by Clemmesen et al. (56), present an unusual opportunity for evaluating the effect of improvement in diagnosis on the time trend. In the Copenhagen tuberculosis referral service, used extensively by local physicians, where diagnostic standards and procedures including systematic bronchoscopy remained virtually unchanged between 1941 and 1950, the lung cancer prevalence rate among male examinees increased at a rate comparable to that recorded by the Danish cancer registry for the total male population.

The rising trend for lung cancer during the past 15 years thus is well documented. The increasing frequency of lung cancer found at necropsy from 1930 onward, while of itself not decisive, when considered in the light of recent events reported by cancer registers, would support the conclusion that the rise in lung cancer did not begin in the 1940 decade, but was a continuation of a trend begun earlier.

CARCINOGENESIS

Tobacco and tobacco smoke contain a complex mixture of hundreds of different chemical components among which are (a) numerous *polycyclic aromatic hydrocarbons* and (b) *inorganic compounds*. Many of these compounds have been shown to be carcinogenic in animals. For information on other components of tobacco and tobacco smoke see Chapter 6.

Before considering the biological evidence available for the carcinogenic effect of these components of tobacco and tobacco smoke, it may be helpful to review briefly some basic principles of carcinogenesis.

Fundamental Problems in Carcinogenesis in Relation to Induction of Neoplastic Changes in Man by Tobacco Smoke

Carcinogenesis is a complex process. Many factors are involved. Some are related to the host, others to the agents. The host factors include genetic, strain, and organ differences in sensitivity to given agents; hormonal and other factors which modify sensitivity of cells; and nutritional state (123).

The character of the agents involved in carcinogenesis varies greatly. Some agents by themselves cause irreversible alterations in cells which may

lead to the production of cancer; others promote the carcinogenic process (21, 33). The former are called *initiators*, the latter *promoters*. Some substances, such as urethan, can be both.

Several classes of chemicals are known to be capable of inducing cancers (143). The chemical properties, the physical state of a substance, and the vehicle in which the substance is introduced into the body can influence the carcinogenic potency of environmental agents, e.g., insertion of a plastic membrane into tissues can cause a cancer (2, 261, 347), but a fine powder of the same plastic has not done so (257). Carcinogens vary with respect to organ affinity and mechanism of inducing a neoplastic change.

There is mounting evidence that viruses may also play an important role in the induction of tumors (137, 140, 345).

It follows from these considerations that failure to produce cancer in a given test, by a given material, does not rule out the carcinogenic capacity of the same material in another species or in the same species when applied under different circumstances. Conversely, induction of cancer by a compound in one species does not prove that the test compound would be carcinogenic in another species under similar circumstances. Therefore, tests for carcinogenicity in animals can provide only supporting evidence for the carcinogenicity of a given compound or material in man. Nevertheless, any agent that can produce cancer in an animal is suspected of being carcinogenic in man also.

The types of cancers produced by the polycyclic aromatic hydrocarbons and other carcinogens depend on the tissues with which they make contact.

Carcinogenesis can be initiated by a rapid single event, best exemplified by the carcinogenic effect of a split-second exposure to ionizing radiations (e.g., from atomic detonation) (40, 351). More often, however, it appears to be characterized by a slow multi-stage process, preceded by non-specific tissue changes, as exemplified by cancers arising in burns. Evidence is presented in another section of this Report that cancer of the lung in cigarette smokers, as well as experimental cancer induced by presumed carcinogens in smoke, is preceded by distinct histologic alterations which can progress to the development of "cancer in situ." These need not proceed to the formation of invasive cancer, and may regress following removal of the stimulus.

The character of "precancerous" change varies in different organs, e.g., in the bladder it is manifested by the formation of "benign" papillomas; in the oral cavity, by the formation of white patches of thickened squamous epithelium—leukoplakia—a non-neoplastic reversible change. The evolved cancer is also subject to further changes. Often, rapidly growing variants develop, a process termed *progression* (119).

Almost every species that has been adequately tested has proved to be susceptible to the effect of certain polycyclic aromatic hydrocarbons identified in cigarette smoke and designated as carcinogenic on the basis of tests in rodents. Therefore, one can reasonably postulate that the same polycyclic hydrocarbons may also be carcinogenic in one or more tissues of man with which they come in contact.

Experimental studies have demonstrated the presence of substances in tobacco and smoke which themselves are not carcinogenic, but can promote

carcinogenesis or lower the threshold to a known carcinogen. There is also some evidence for the presence of anticarcinogenic substances in tobacco and tobacco smoke (107).

Threshold

In any assessment of carcinogenicity, dosage requires special consideration. The smallest concentration of benzo(a)pyrene known to induce carcinoma when dissolved in acetone and applied to the skin of mice three times weekly is 0.001 percent (380). Subcutaneous cancer follows injection of only 0.00195 mg. of benzo(a)pyrene in 0.25 ml. tricaprylin. Whether there is a threshold for effective dosage of a carcinogenic agent is controversial at the present time. The evidence for the existence of a threshold has been summarized by Brues (43). When pulmonary tumors were induced in mice with dibenzanthracene and urethan by Heston et al. (172, 232), a linear response was demonstrated at higher doses but a curvilinear response appeared at lower doses. At extremely low dosage, the possible effect of the agent became obscured by the incidence of spontaneous pulmonary tumors. In the case of induction of cancer by ionizing radiation, it has been claimed that there is no threshold (210). It is conceivable that there is no threshold for certain neoplasms, whereas there may be one for others.

Neither the available epidemiologic nor the experimental data are adequate to fix a safe dosage of chemical carcinogens below which there will be no response in man (43, 172, 210, 232).

Carcinogenicity of Tobacco and Tobacco Smoke in Animals

There is evidence from numerous laboratories (31, 42, 92, 93, 105, 132, 139, 263, 296, 297, 338, 372, 373, 382, 383) that tobacco smoke condensates and extracts of tobacco are carcinogenic for several animal species. Several laboratories obtained negative results (154, 262, 267, 268).

The nature of the test system is critical in studies on carcinogenic activity of such complex mixtures. The relatively high susceptibility of mouse skin to carcinogenic hydrocarbons has made it a favorite test object (6, 278). A second test system also used is the induction of pulmonary adenomas in mice. This will be detailed in the section on Experimental Pulmonary Carcinogenesis. A third system which has been used less frequently is the induction of subcutaneous sarcomas in the rat whose connective tissues have been found to be susceptible to the carcinogenic action of many different chemicals as well as of complex materials. Another test, which has been used in some studies and can be read within five days after painting the skin of mice with a carcinogen, consists of determining the number of sebaceous glands and the thickness of the epidermis (342a). However, the reliability of this procedure as a bio-assay for carcinogenesis is open to question.

Skin

Many investigators have shown that the application of tobacco tar to the skin of mice and rabbits induces papillomas and carcinomas (31, 42, 92, 93,

105, 132, 139, 263, 296, 297, 338, 372, 373, 382, 383). Wynder et al. (382) applied a 50 percent solution of cigarette smoke condensate in acetone three times weekly to the shaved backs of mice so that each received about 10 gm. yearly. The animals were usually painted for 15 months. More than 5 gm. annually was required for the induction of epidermoid carcinoma and more than 3 gm. for the induction of papillomas (372, 373). Since the carcinogenic potency of a smoke condensate can be altered by varying conditions of pyrolysis, the manner of preparation of the tar is of importance (392). This may be one reason for the negative reports (154, 262, 267, 268) encountered in the literature. Extracts of tobacco usually have weaker carcinogenic activity than do the condensates of cigarette smoke (93, 390).

Gellhorn (126) and Roe et al. (290, 293) have reported that condensates of cigarette smoke have cocarcinogenic or promoting properties. It was found that the application of a mixture of benzo(a)pyrene plus condensate of cigarette smoke to the skin of mice resulted in the production of many neoplasms, whereas the same concentration of benzo (a) pyrene alone failed to elicit tumors. Gellhorn (126) found that the tobacco smoke condensate appeared to accelerate the transformation of papillomas to carcinomas. Anticarcinogens have also been reported in condensates of cigarette smoke (107).

Nicotine is not usually considered a carcinogen on the basis of animal experiments (346, 391). Removal of nicotine or other alkaloids did not diminish the carcinogenicity of condensates of smoke for the skin of mice. The induction of pulmonary adenomas in mice by urethan (120) and of skin tumors in mice by ultraviolet radiation (121) are not altered by the administration of nicotine or some of its oxidation products.

Subcutaneous Tissue

Druckrey (92) found that cigarette smoke condensates or alcoholic extracts of cigarette tobacco regularly induced sarcomas in rats at the site of subcutaneous injections. The material was injected once weekly for 58 weeks, the total dose administered being 3.2 gm. The animals were followed, thereafter, until death. Approximately 20 percent of the animals in each experiment developed the neoplasms. Druckrey also carried out similar experiments with benzo(a)pyrene and found that the amount of this polycyclic aromatic hydrocarbon in smoke condensates or tobacco extracts cannot account for more than a few percent of the activity of the tobacco products. This same discrepancy between the quantity of benzo(a)pyrene in smoke condensates and the carcinogenic potency of the condensates has been reported by several investigators using the mouse skin test (92, 93, 126, 372, 390).

Mechanism of the Carcinogenicity of Tobacco Smoke Condensate

Tobacco smoke contains many carcinogenic polycyclic aromatic hydrocarbons (Table 2, Chapter 6). Benzo(a)pyrene is present in much larger concentrations than is any other carcinogenic polycyclic hydrocarbon. The inability to account for the carcinogenicity of the tobacco products, except to a very minor degree, by the amount of benzo(a)pyrene present was unanticipated. Both Druckrey (92) and Wynder (372) emphasized that

the benzo(a)pyrene concentration of various tobacco and smoke preparations is only sufficient to account for a very small part of the carcinogenicity of these materials. One hypothesis suggests that promoting agents present in tobacco and tobacco smoke, such as various phenols, enhance the potency of the carcinogenic hydrocarbons so as to account for the biological activity of the tobacco products. Further, possible synergism between low levels of the several known carcinogens in the tobacco condensates and extracts may also enhance the carcinogenic potency.

Other Materials of Possible Importance in Carcinogenicity

PESTICIDES

Pesticides currently used in the husbandry of tobacco in the United States include DDT, TDE, aldrin, dieldrin, endrin, chlordane, heptachlor, malathion and occasionally parathion (see Chapter 6). The first two are used more commonly than the others nearer the time for harvesting. TDE has been detected in tobacco and its smoke (242), and endrin has been extracted from tobacco on the market (34, 35). Aldrin and dieldrin have been found to increase the incidence of hepatomas in mice of the C3HeB/Fe strain (68). Aldrin is metabolized to dieldrin, and the effect may be due only to the latter or some subsequent metabolite. DDT has been shown to induce hepatomas in trout (153) and rats (253). The possible role of these compounds in contributing to the potential carcinogenicity of tobacco smoke is not known (see also Chapter 6, section on Pesticides).

LACTONES

The lactones have been suggested as contributors to the carcinogenic effects of tobacco. Attention was focused on these compounds by the discovery (74, 74A, 291, 292, 362) that β-propiolactone, used as a sterilant and preservative, is carcinogenic for mice. Coumarin, a δ-lactone, has been used as a common flavoring in tobacco. Hydroxy- and methoxy-coumarins are constituents of the leaf itself and are carried over in the smoke. Also the γ-lactone, β-levantenolide, is present in both tobacco and smoke (354). The following lactones (not suggested to be present in tobacco) have been found to be carcinogenic for animals: γ-lactones (patulin, penicillic acid, methyl protoanemonin) and δ-lactones (parasorbic acid lactone and aflatoxins).

RADIOACTIVE COMPONENTS

Potassium 40, a β-emitter, has been reported to be a source of radioactivity in cigarette smoke. The amounts of this activity taken into the lung, even by the heavy smoker, are minute when compared with the daily uptake of K 40 from the diet. Furthermore this material is highly soluble and it is rapidly eliminated from the lung tissue thereby preventing any local build-up (300a). The α-particle activity due to the radium and thorium content of tobacco smoke, even for the heavy smoker, is less than one percent of the atmospheric radon and thoron inhaled daily by any individual (347a). A recent but still unpublished report holds that Po 210 is the major source of radioactivity in cigarette smoke. The amounts calculated to be absorbed are high enough to merit further study as a possible factor in carcinogenesis (282a). No data

appear to have been published on the uptake by the tobacco plant of radioactive constituents from fall-out (e.g., Strontium 90 and Cesium 137).

Summary

Condensates of tobacco smoke are carcinogenic when tested by application to the skin of mice and of rabbits, by subcutaneous injection in rats, and by painting the bronchial epithelium of dogs. The amount of known carcinogens in cigarette smoke is too small to account for their carcinogenic activity. Promoting agents have also been found in tobacco smoke but the biological action of mixtures of the known carcinogens and promoters over a long period of time is not understood.

Carcinogenesis in Man

Despite the many uncertainties in the application to man of research results in animals, the animal data serve a purpose in indicating potential carcinogenicity. The greatest consistency is observed in respect to those groups of chemical compounds which are carcinogenic in many species. Several of the polycyclic aromatic hydrocarbons present in tobacco smoke fall into this category in that they are carcinogenic for most animal species tested. Since the response of most human tissues to exogenous factors is similar qualitatively to that observed in experimental animals, it is highly probable that the tissues of man are also susceptible to the carcinogenic action of some of the same polycyclic aromatic hydrocarbons. The results of exposing humans to pure polycyclic aromatic hydrocarbons or to natural products containing such compounds have been reviewed by Falk et al. (108).

Polycyclic Aromatic Hydrocarbons

Cancer induction in man by the application of "pure" polycyclic aromatic hydrocarbons has not been reported. Klar (188) reported an epithelial tumor on his left forearm that appeared three months after termination of an experiment in which mice were painted with 0.25 percent benzo(a)pyrene in benzene. Cottini and Mazzone (63) applied 1.0 percent benzo(a)pyrene in benzene to the skin of 26 volunteers in daily doses and observed the sequential development of erythema, pigmentation, desquamation, and verrucae. The changes were more pronounced in older than in younger volunteers. After 120 applications, the experiment was terminated and the lesions regressed within three months. Rhoads et al. (286) described similar changes in human skin painted with the same carcinogen. These reversible changes were similar to the initial changes in the skin of men who ultimately developed invasive cancers following industrial exposure to carcinogens. Cancer of the skin of the fingers has not been reported in cigarette smokers, despite the intense discoloration so often seen at this site (212). However, spontaneous cancer of the skin of the fingers is very rare.

Industrial Products

SOOT

Cancer of the scrotum in chimney sweeps subjected to prolonged massive exposure to soot was a common finding in the eighteenth century (279). As many as one in every ten men engaged in this occupation developed cancers (204). Sporadic cases of cancer of the skin at other sites, such as the face (60), the ear, and the penis (264), were also described. The neoplasms usually occurred in men between 18 and 47 years of age (213), possibly reflecting the early age at which boys entered this occupation. Whether there is an increase in cancer in persons *now* working in industries involving exposure to "carbon black" is being debated (108). The chemical and physical properties of "carbon black" vary widely (109, 110).

As early as 1922, Passey (266) found that cancer of the skin could be produced experimentally by extracts of soots. More recently, Falk et al. (111) showed that polycyclic hydrocarbons in the "carbon black" were present in processed rubber, and rubber extracts were found to be carcinogenic for the skin of mice. Also Falk and Steiner (109, 110) found furnace-type black rich in pyrene, fluoranthene, benzo(a)pyrene, benzo(e)pyrene, anthanthrene, benzo(g, h, i)perylene, and coronene in particles having an average diameter of 80 mμ or larger. These compounds were not present in channel blacks which have smaller particle size. The amount of benzo(a)pyrene extracted from different soots varies from none to 2 mg. per gm. (307).

COAL TAR AND PITCH

Butlin (50) in 1892 described cancer of the skin as an occupational hazard in the coal tar industry. The distillation of coal tar yields many different organic compounds with a residue of pitch containing polycyclic aromatic hydrocarbons (300). Henry (166) reported that up to 1945, 2,229 of 3,753 cases of industrial skin cancer studied were attributed to exposure to tar and pitch, the remainder to mineral oils. The latent period for induction of this type of cancer is estimated to be 15 to 25 years. Most reports about this type of cancer have come from England (166), but they have also appeared from other countries (44, 73, 231, 310). Bonnet (32) reported an interesting case of pulmonary cancer in a workman exposed to hot tar containing three percent benzo(a)pyrene. He estimated that 320 μg. of the carcinogenic hydrocarbon could have been inhaled hourly. Carcinogenicity of both creosote oil and anthracene oil for the skin of workmen has been documented (18, 39, 259).

MINERAL OILS

So-called paraffin cancer is not caused by paraffin but by exposure to impurities in oils used in the process of purification (165, 203). Recent work (321) has confirmed the view that refined paraffin wax does not contain polycyclic aromatic hydrocarbons and that it is not carcinogenic.

The danger incidental to exposure to mineral oils has been decreased by extraction of carcinogenic hydrocarbons with sulfuric acid (164). Bioassay of mineral oils indicates that their content of carcinogens varies with their

geographic origin (348). Animal tests show that the carcinogenicity of mineral oil increases as the temperature of distillation increases or when cracking is instituted for the formation of new compounds. A variety of carcinogenic compounds has been isolated from different fractions. Some fractions presumably free from benzo(a)pyrene have nevertheless been found to be carcinogenic. Coal tar contains 0.3 to 0.8 percent benzo(a)pyrene, soot 0.03 percent, and American shale oil 0.003 to 0.004 percent (51).

SUMMARY

There is abundant evidence that cancer of the skin can be induced in man by industrial exposure to soots, coal tar and pitch, and mineral oils. All of these contain various polycyclic aromatic hydrocarbons proven to be carcinogenic in many species of animals. Some of these hydrocarbons are also present in tobacco smoke. It is reasonable to assume that these can be carcinogenic for man also.

CANCER BY SITE

The seven prospective studies described and summarized in Chapter 8 provide a natural point of departure for considering the relative risks, for smokers and non-smokers, of cancer at specific sites. The consolidated findings (Table 1) identify eight sites as displaying higher risks of cancer among cigarette smokers, who in recent decades have been the predominant consumers of tobacco. These sites are lung, larynx, oral cavity, esophagus, urinary bladder, kidney, stomach, and prostate. The mortality ratios for cigarette smokers *vis-a-vis* non-smokers range in descending order from nearly 11 to 1 for cancer of the lung and bronchus to 1.3 to 1 for prostatic cancer. For five of these sites—lung, larynx, oral cavity, esophagus, and urinary bladder—cigarette smokers have a substantially higher cancer risk than non-smokers.

The smaller excess risks among cigarette smokers for cancer of the stomach, prostate, and kidney deserve comment. The prospective studies are not in complete accord as to an association with smoking history for cancer of the prostate and kidney, and in some of the studies which were conducted with other objectives in mind, the relationships of prostatic and renal cancer with smoking history represent incidental findings. No other evidence can be adduced in evaluating and interpreting the prostatic and renal mortality ratios, since the effects were not large enough to draw the attention of investigators. For these reasons, cancer of the prostate and kidney will not be discussed further at this time. This decision does not imply a conclusion that the findings must be artifacts, but rather that judgment on these sites should be suspended until more data become available.

The case for considering cancer of the stomach in more detail is not much stronger than for prostate and kidney, but the consistency among the prospective studies is better. In addition, the studies report a stronger association of smoking history with stomach ulcer. Clinical impressions of this relation-

TABLE 1.—*Expected and observed deaths and mortality ratios of current smokers of cigarettes only, for selected cancer sites, all other sites, and all causes of death; each prospective study and all studies*

Site of cancer		British doctors	Men in 9 States	United States veterans	California occupational [1]	California Legion [1]	Canadian veterans	Men in 25 States [1]	Total
Lung and bronchus, 162-3 [2]	Observed	129	233	519	138	98	317	399	1,833
	Expected	6.4	23.4	43.3	8.7	19.9	27.1	41.5	170.3
	Ratio	20.2	10.0	12.0	15.9	4.9	11.7	9.6	10.8
Larynx, 161	Observed	7	17	14	3	6	5	23	75
	Expected	0.0	1.3	2.4	0.0	4.0	0.0	6.3	14.0
	Ratio	---	13.1	5.8	---	1.5	---	3.7	5.4
Oral Cavity, 140-8.	Observed	6	22	54	7	10	20	33	152
	Expected	0.0	7.8	8.1	7.2	5.2	5.1	3.6	37.0
	Ratio	---	2.8	6.6	1.0	1.9	3.9	9.2	4.1
Esophagus, 150	Observed	7	18	33	4	9	22	20	113
	Expected	3.3	2.7	5.2	5.5	1.8	6.8	8.4	33.7
	Ratio	2.1	6.6	6.4	0.7	5.1	3.3	2.4	3.4
Bladder, 181	Observed	12	41	55	13	7	38	50	216
	Expected	13.9	17.2	31.4	2.2	1.8	22.3	22.8	111.6
	Ratio	0.9	2.4	1.8	6.0	4.0	1.7	2.2	1.9
Kidney, 180	Observed	8	21	34	10	6	13	28	120
	Expected	0.0	14.0	23.1	0.0	8.3	9.5	24.1	79.0
	Ratio	---	1.5	1.5	---	0.7	1.4	1.2	1.5
Stomach, 151	Observed	31	76	90	24	25	76	91	413
	Expected	28.3	33.7	61.5	31.4	20.5	41.2	68.6	285.2
	Ratio	1.1	2.3	1.5	0.8	1.2	1.9	1.3	1.4
Prostate, 177	Observed	15	51	106	4	19	48	75	318
	Expected	29.0	32.4	53.7	8.6	22.1	32.3	74.9	253.0
	Ratio	0.5	1.6	2.0	0.5	0.9	1.5	1.0	1.3
All Other Sites	Observed	116	290	671	141	106	237	571	2,132
	Expected	112.0	228.3	505.7	109.4	120.6	192.1	423.8	1,692.0
	Ratio	1.0	1.3	1.3	1.3	0.9	1.2	1.3	1.3
All Causes of Death.	Observed	1,672	3,781	7,236	1,456	1,264	4,001	6,813	26,223
	Expected	1,161.8	2,227.7	4,043.1	818.5	799.4	2,420.1	4,183.3	15,653.9
	Ratio	1.44	1.70	1.79	1.78	1.58	1.65	1.63	1.68

[1] Includes all cigarette smokers (current and ex-smokers).
[2] International Statistical Classification number.

ship undoubtedly stimulated some of the case-control studies of smoking and stomach cancer which have been reported. Stomach cancer incidence and mortality have been declining rapidly in the United States in recent years, simultaneously with the rise in lung cancer. This and the presence of additional evidence from retrospective studies justify reviewing stomach cancer in more detail in this chapter.

Thus the six cancer sites to be reviewed here are lung, larynx, oral cavity, esophagus, urinary bladder, and stomach.

LUNG CANCER

Historical

The earliest suspicions of an association between smoking and lung cancer were undoubtedly evoked by the provocative clinical observations that lung cancer patients were predominantly heavy smokers of tobacco. Early investigators, including Müller (250) in 1939 and Schairer and Schoeniger (309)

in 1943, were impressed not only with the clinical observations of a high proportion of tobacco smokers among lung cancer patients but also with the rise in the percentage of lung cancers in autopsy series in Cologne and Jena. Among the early observations in the United States were those of Ochsner and DeBakey (258) who were impressed by the probable relationship between cigarette smoking and lung cancer. The initial observations prior to Müller's work were not, however, corroborated by surveys including controls without lung cancer.

As early as 1928, Lombard and Doering (221) in a study of cancer patients' habits in Massachusetts, wrote that "any study of the habits of individuals with cancer is of little value without a similar study of individuals without cancer." Their analysis of 217 cases of cancer and 217 controls identified, among other things, an association between heavy smoking (all types combined) and cancer in general, and between pipe smoking and oral cancer in particular. The pipe smokers then constituted the bulk (73.1 percent) of the heavy smokers. This is of historical interest in relation to the present-day percentage of heavy cigarette smokers. Furthermore, since there were but five lung cancers in Lombard's test group in an era before much of the rise in lung cancer incidence had occurred, the data were not adequate to demonstrate an association between lung cancer and cigarette smoking.

Probably the first study designed to explore this association systematically was by Müller in 1939 (250) who had noted the increase in percentage of primary carcinomas of the lung being diagnosed at autopsy between the years 1918 and 1937 in Cologne, an increase almost entirely in males. Although considering other variables as possibly related to the rise in lung cancer mortality, such as increases in street dusts, automobile exhaust gases, war gas exposure in World War I, increased use of X-rays, influenza, trauma, tuberculosis, and industrial growth (air pollution?), he took special cognizance of the preponderant increase of lung cancer among males and the parallel rise in tobacco consumption from shortly before and since World War I and selected this variable for study. In what appears to be a carefully conducted inquiry of smoking habits in a series of 86 lung cancer patients and 86 apparently healthy controls, matched by age, a significant excess of heavy smokers was observed among the lung cancer patients.

In the next ten years, three more case-control studies or comparisons with cancers of other sites reached the literature (280, 309, 363) and from 1950 to the present time 25 additional retrospective (38, 82, 138, 147, 150, 152, 192, 199, 207, 211, 222, 236, 238, 277, 283, 301, 311, 314, 316, 335, 337, 365, 375, 379, 381) and 7 prospective studies (25, 83, 84, 87, 88, 96, 97, 157, 162, 163) were undertaken.

Retrospective Studies

The 29 retrospective studies of the association between tobacco smoking and lung cancer are sumarized in Tables 2 and 3. As these tables suggest, the studies varied considerably in design and method. Methodologic variations have occurred in the omission, inclusion, or treatment of the following: