Chapter 9

Cancer

Contents

Figures

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

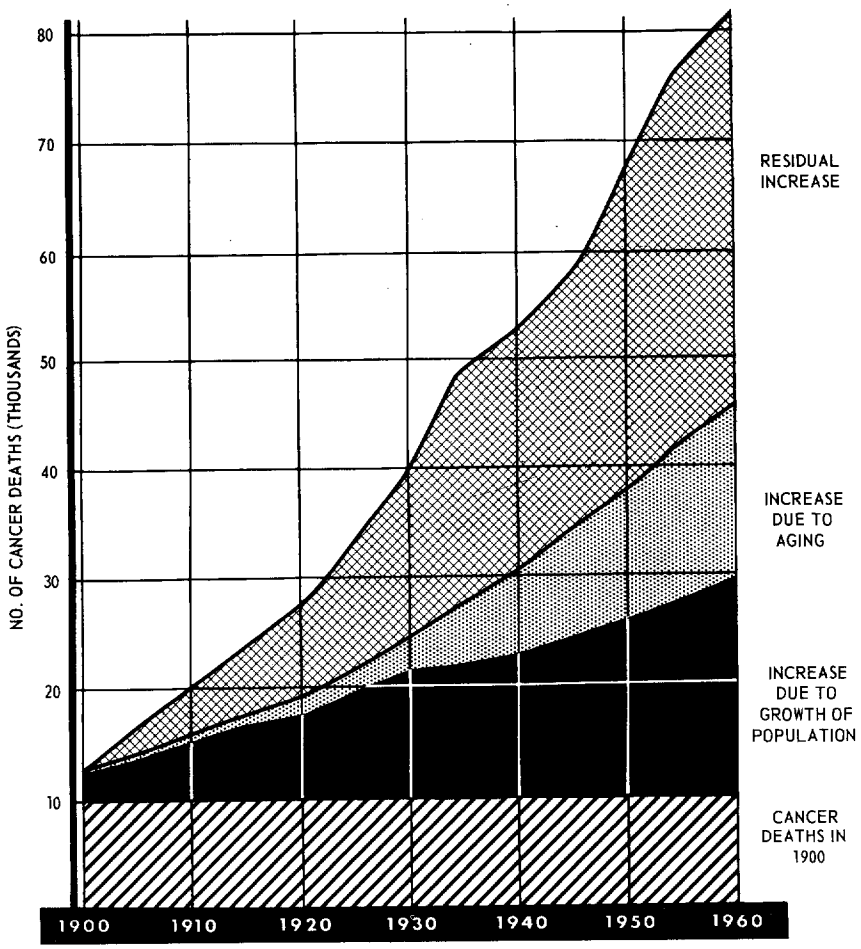


FIGURE 1.

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]

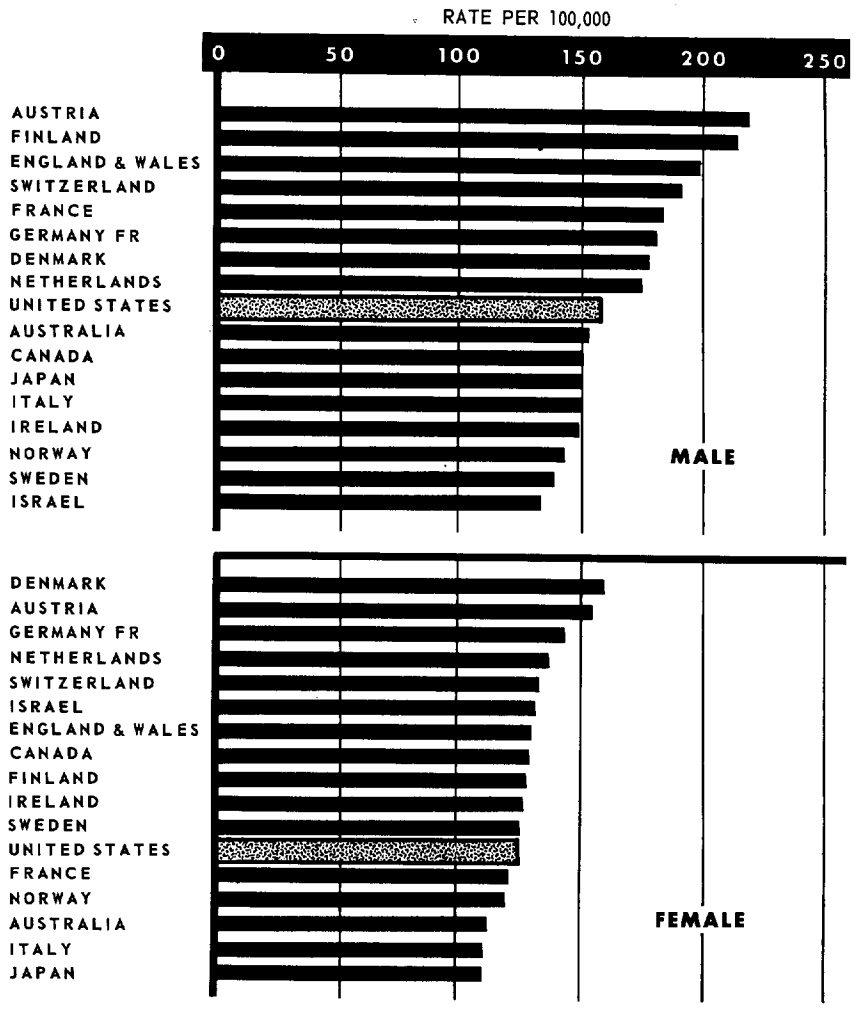


FIGURE 2.

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.

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

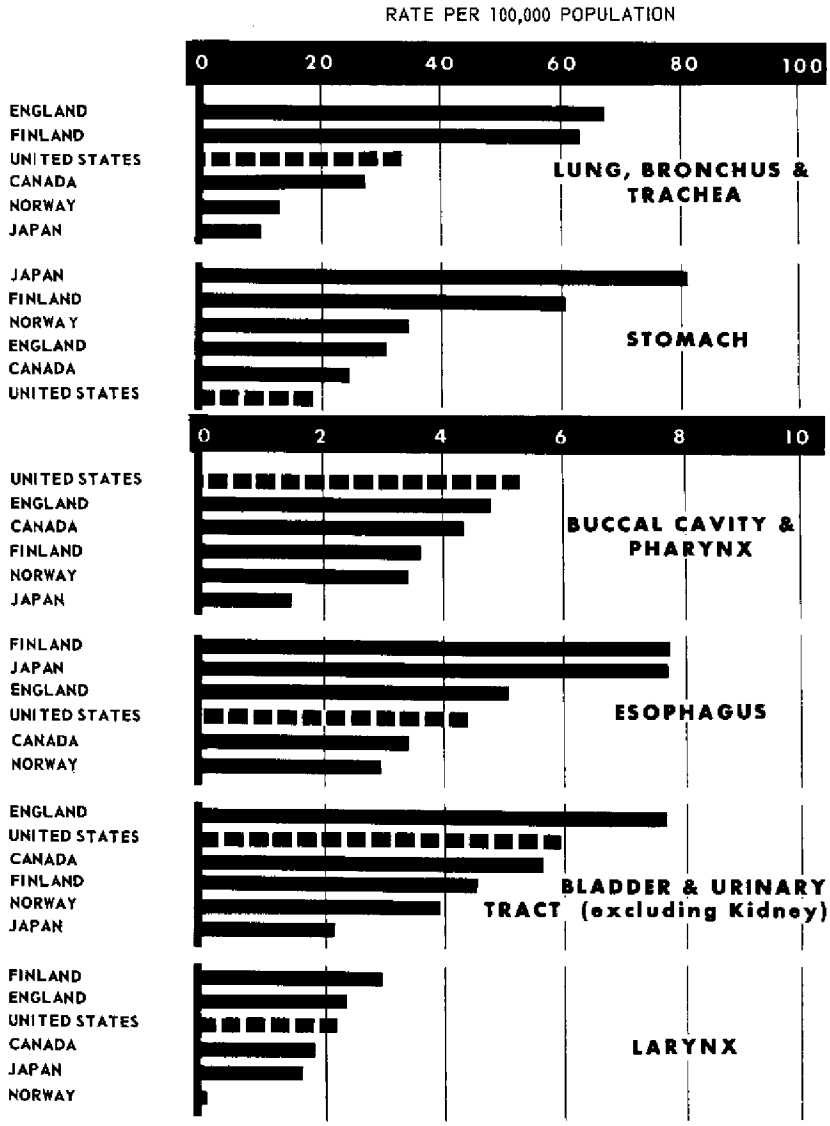


FIGURE 3A.

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]

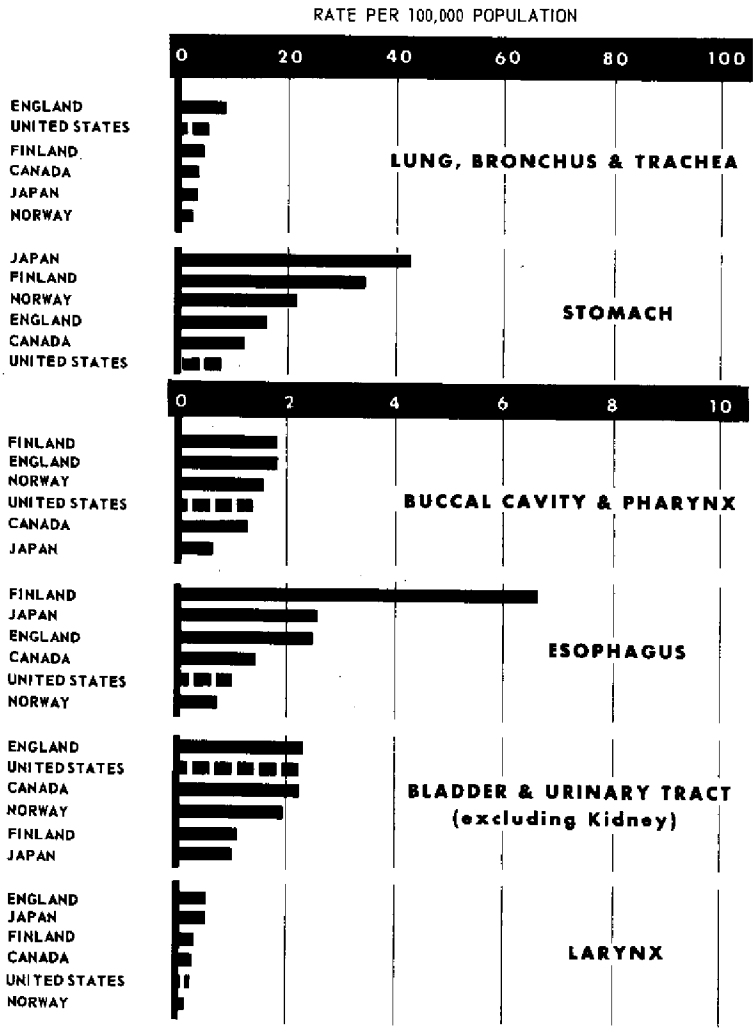


FIGURE 3B.

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 differ.

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.

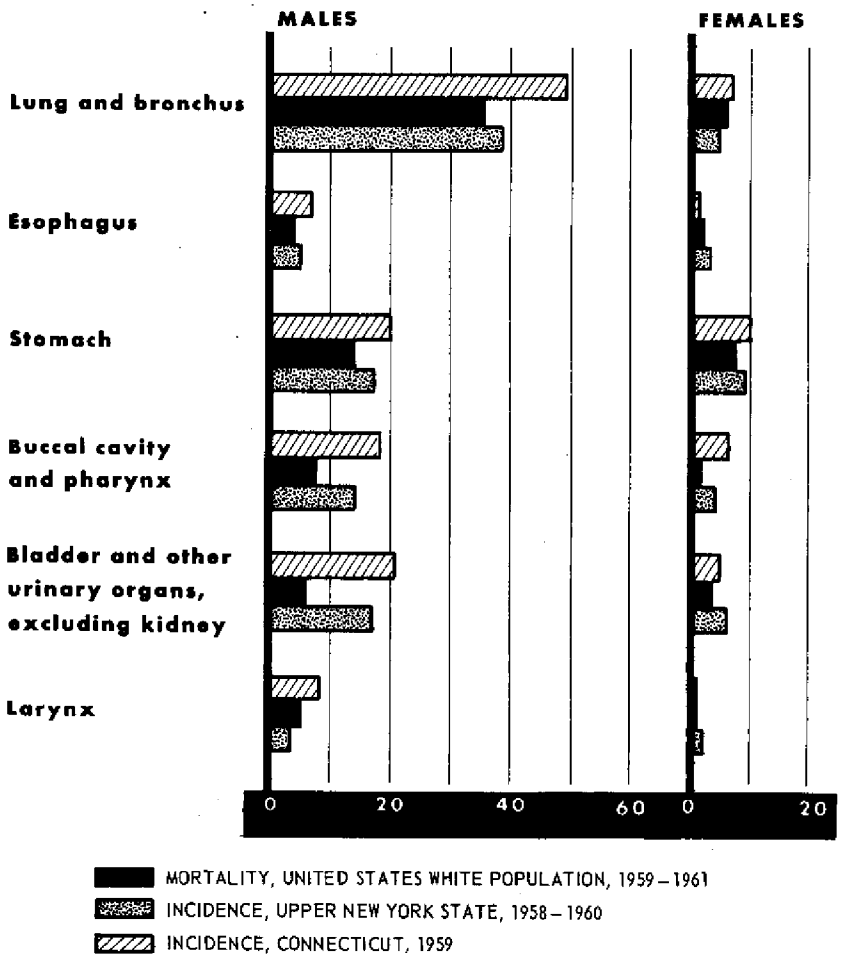


FIGURE 4.

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:

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).

	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

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]

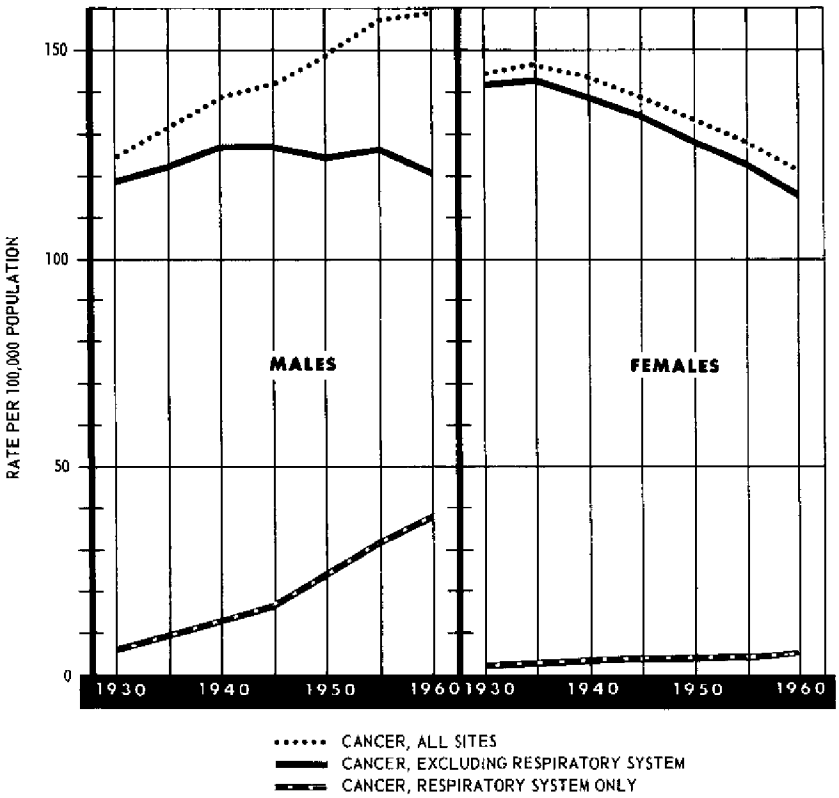


FIGURE 5.

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]

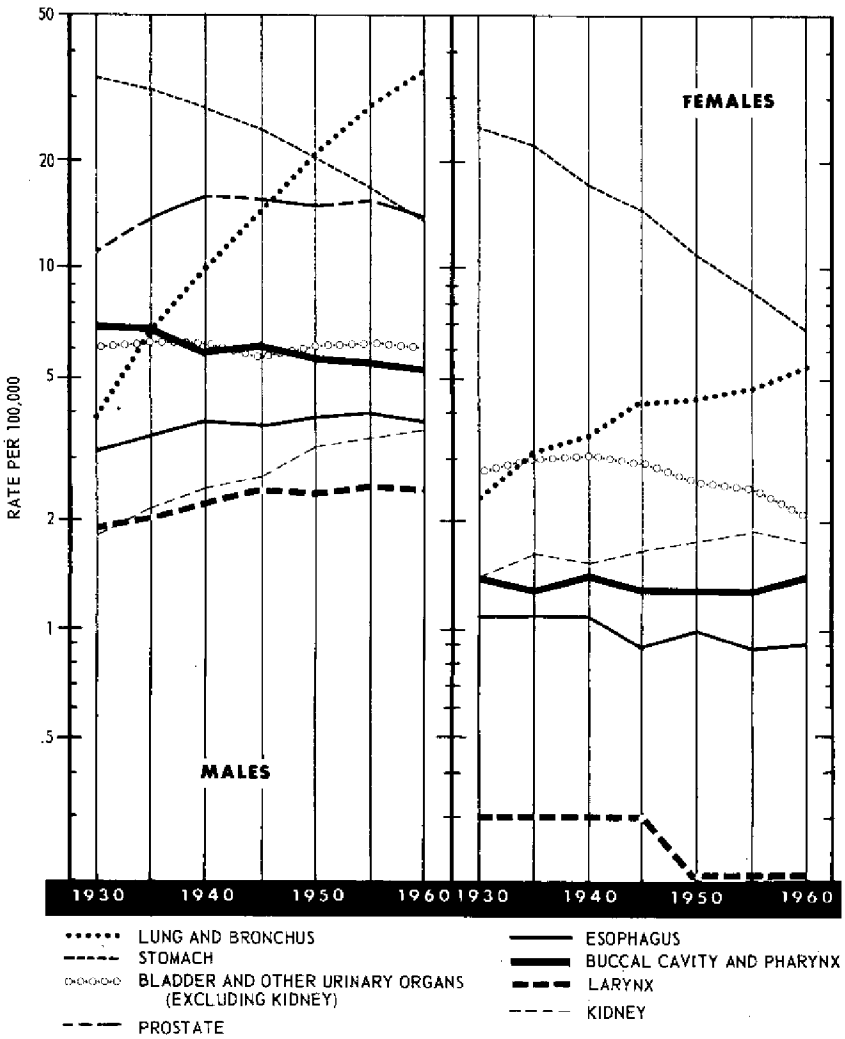


FIGURE 6.

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 horn 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]

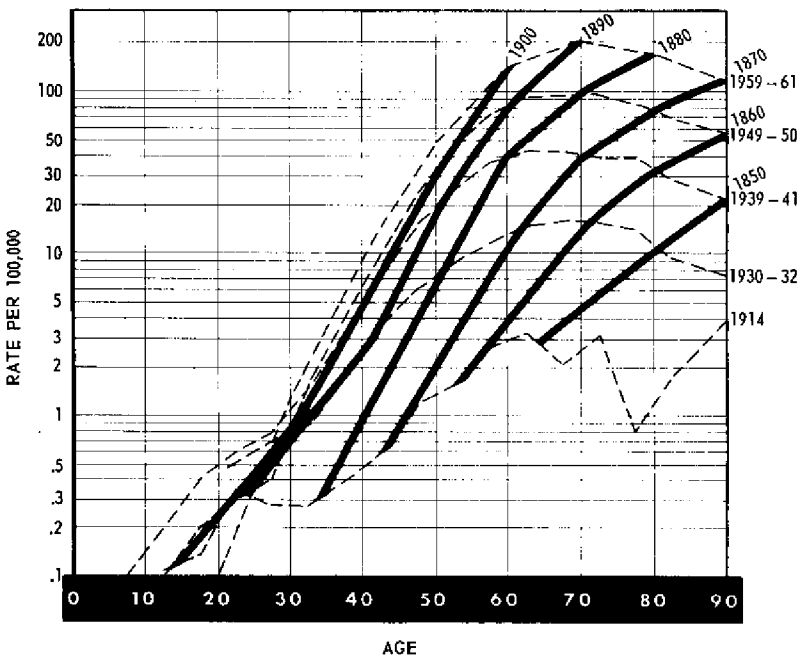


FIGURE 7.

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 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)

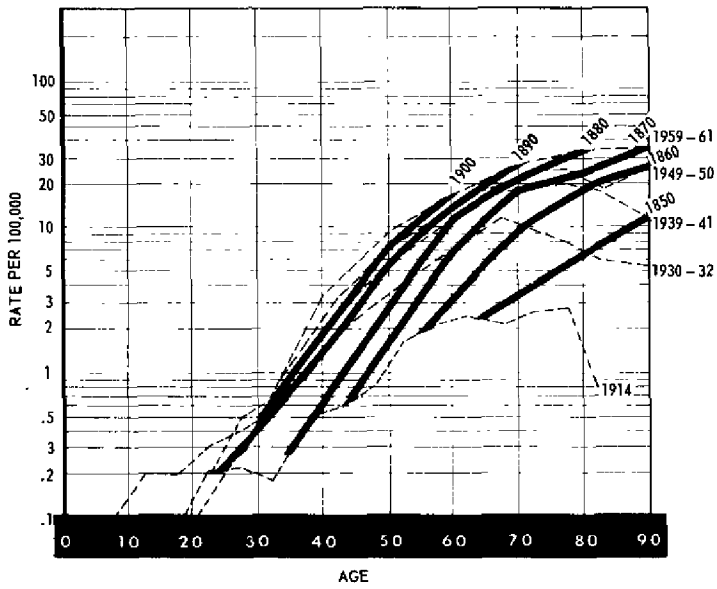


FIGURE 8.

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 processs. 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 he 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 bums. 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 dihenzanthracene 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 bioassay 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 ß-propiolactone, used as a sterilant and preservative, is carcinogenic for mice. Coumarin, a &-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 y-lactone, ß-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: y-lactones (patulin, penicillic acid, methyl protoanemonin) and -lactones (parasorbic acid lactone and aflatoxins).

RADIOACTIVE COMPONENTS

Potassium 40, a ß-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 a-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 carcinogenie 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.

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 Iung 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 comhined) 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 he 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:

METHODOLOGIC VARIABLES

Subject Selection—

1. Males and/or females
2. Occupational groups
3. Hospitalized cases
4. Autopsy series
5. Total lung cancer deaths in an area
6. Samplings of nationwide lung cancer deaths

Control Selection—

1. Age matching vs. age groups
2. Healthy individuals
3. Patients hospitalized for other cancers
4. Patients hospitalized for causes other than cancer
5. Deaths from cancers of other sites
6. Deaths from other causes than cancer
7. Samplings of the general population

Method of Interviewing—

1. Mailed questionnaires
2. Personal interviewing of subjects (or relatives) and controls
   a) By professional personnel
   b) By non-professional personnel

Tobacco-use Histories—

1. By type of smoking (separately and combined)
2. By amount and type
3. By amount, type, and duration
4. By inhalation practices

Other Variables Concurrently Studied—

1. Geographic distribution
   a) Regional
   b) Urban-rural
2. Occupation
3. Marital status
4. Coffee and alcohol consumption
5. Other nutritional factors
6. Parity
7. War-gas exposures
8. Other pathologic conditions
9. Hereditary factors
10. Air pollution
11. Previous respiratory conditions

This listing of methodologic variations is by no means complete, nor does it imply that the individual retrospective studies should be criticized for their choice of study methods and factors for observation. The individual points of criticism have usually applied to one or two studies but not to all.

It is indeed striking that every one of the retrospective studies of male lung cancer cases showed an association between smoking and lung cancer. All have shown that proportionately more heavy smokers are found among the lung cancer patients than in the control populations and proprtionately fewer non-smokers among the cases than among the controls. Furthermore, the disparities in proportions of heavy smokers between "test" groups and controls are statistically significant in all the studies. The differences in proportions of non-smokers among the two groups are also statistically significant in all studies but one (236) ; in the latter study. although there were fewer non-smokers among lung cancer patients, the difference was very small.

In the studies which dealt with female cases of lung cancer, similar findings are noted in all of them with one exception (238). In this latter study, although significantly more heavy smokers were found among the lung cancer cases than among the controls, the proportion of non-smokers among the cases was distinctly higher than among the controls. This is the only inconsistent finding among all the retrospective studies. Its meaning is not clear but the authors have indicated that non-response among their female cases was 50 percent.

The weight to be attached to the consistency of the findings in the retrospective studies is enhanced when one considers that these studies exhibit considerable diversity in methodologic approach.

TABLE 2.—*Outline of methods used in retrospective studies of smoking in relation to lung cancer*

Investigator, year, and reference	Country	Sex of cases	Number of persons and method of selection		Collection of data
			Cases	Controls	
Müller 1939 (250)	Germany	M	86 Lung cancer decedents, Bürger Hospital, Cologne.	86 Healthy men of the same age	Cases: Questionnaire sent to relatives of deceased. Controls: Not stated.
Schairer and Schoeniger 1943 (309).	Germany	M	93 Cancer decedents autopsied at Jena Pathological Institute, 1930–1941.	270 Men of the city of Jena aged 53 and 54 (average age of lung cancer victims = 53.9).	Cases: Questionnaire sent to next of kin (195 for lung cancer). Controls: Questionnaire sent to 700.
Potter and Tully 1945 (280)	U.S.A.	M	43 Male patients aged over 40 in Massachusetts cancer clinics with cancer of respiratory tract.	1,847 Patients of same group with diagnoses other than cancer.	Cases and controls interviewed in clinics
Wassink 1948 (363)	Netherlands	M	134 Male clinic patients with lung cancer.	100 Normal men of same age groups as cases.	Cases: Interviewed in clinic. Controls: Not stated.
Schrek et al., 1950 (311)	U.S.A.	M	82 Male lung cancer cases among 5,003 patients recorded, 1941–48.	522 Miscellaneous tumors other than lung, larynx and pharynx.	Smoking habits recorded during routine hospital interview.
Mills and Porter 1950 (237)	U.S.A.	M	444 Respiratory cancer decedents in Cincinnati, 1940–45 and in Detroit, 1942–46.	430 Sample of residents matched by age in Columbus, Ohio, from census tracts stratified by degree of air pollution.	Cases: Relatives queried by mail questionnaire or personal visit. Controls: House-to-house interviews.
Levin et al., 1950 (207)	U.S.A.	M	236 Cancer hospital patients diagnosed lung cancer.	481 Patients in same hospital with non-cancer diagnoses.	Cases and controls: Routine clinical history taken before diagnosis.
Wynder & Graham 1950 (381).	U.S.A.	M–F	605 Hospital and private lung cancer patients in many cities.	780 Patients of several hospitals with diagnoses other than lung cancer.	Nearly all data by personal interview; a few cases by questionnaire; a few from intimate acquaintances. Some interviews with knowledge or presumption of diagnosis, some with none.
McConnell et al., 1952 (236)	England	M–F	100 Lung cancer patients, unselected, in 3 hospitals in Liverpool area, 1946–49.	200 Inpatients of same hospitals, matched by age and sex, without cancer, 1948–50.	Personal interviews by the authors of both cases and controls, with few exceptions.
Doll and Hill 1952 (82)	Great Britain.	M–F	1,465 Patients with lung cancer in hospitals of several cities.	1,465 Patients in same hospitals, matched by sex and age group; some with cancer of other sites, some without cancer.	Personal interviews of cases and controls by almoners.
Sadowsky et al., 1953 (301)	U.S.A.	M	477 Patients with lung cancer in hospitals in 4 states.	615 Patients in same hospitals with illnesses other than cancer.	Personal questioning by trained interviewers.

Wynder and Cornfield 1953 (379).	U.S.A.	M	63 Physicians reported in A.M.A. Journal as dying of cancer of the lung.	133 Physicians of same group dying of cancer of certain other sites.	Mail questionnaire to estates of decedents
Koulumies 1953 (192)	Finland	M–F	812 Lung cancer patients diagnosed at one hospital in 16 years.	300 Outpatients of same hospital aged over 40, living in similar circumstances, and without cancer, February and March 1952.	Cases and controls questioned about smoking habits when taking case histories.
Lickint 1953 (211)	Germany	M–F	246 Lung cancer patients in a number of hospitals and clinics.	2,002 Sample of persons without cancer living in the same area and of same sex and age range as cases.	Personal interviews by staff members of cooperating hospitals and clinics, corresponding in time to interviews of cases.
Breslow et al., 1954 (38)	U.S.A.	M–F	518 Lung cancer patients in 11 California hospitals, 1949–52.	518 Patients admitted to same hospitals about the same time, for conditions other than cancer or chest disease, matched for race, sex, and age group.	Cases and controls questioned by trained interviewers, each matched pair by the same person.
Watson and Conte 1954 (365).	U.S.A.	M–F	301 All patients of Thoracic Clinic at Memorial Hospital who were diagnosed lung cancer, 1950–52.	468 All patients of same clinic during same period with diagnoses other than lung cancer.	The 769 consecutive patients of case and control groups were questioned by the same trained interviewer.
Gsell 1954 (138)	Switzerland	M	135 Men with diagnosis of bronchial carcinoma.	135 Similar hospital patients with diagnoses other than lung cancer, and of the same age.	Personal interviews, all by the same person.
Randig 1954 (283)	Germany	M–F	448 Lung cancer patients in a number of West Berlin hospitals, 1952–1954.	512 Patients with other diagnoses, matched for age.	Controls were interviewed at about the same time as the cases, each case-control pair by the same physician.
Stocks and Campbell 1955 (337).	(Preliminary; see 1957 report below.)				
Wynder et al., 1956 (375)	U.S.A.	F	105 Patients with lung cancer in several New York City hospitals, 1953–55.	1,304 Patients at Memorial Center with tumors of sites other than respiratory or upper alimentary, 1953–1955.	Cases: Personal interview or questionnaire mailed to close relatives or friends Controls: Personal interview.
Segi et al., 1957 (316)	Japan	M–F	207 Patients with lung cancer in 33 hospitals in all parts of the country, 1953–55.	5,636 Patients free of cancer in 420 local health centers, selected to approximate the sex and age distributions of cases.	Cases and controls by personal interview using long questionnaire on occupational and medical history and living habits.
Mills and Porter 1957 (238)	U.S.A.	M–F	578 Residents of defined areas dying of respiratory cancer, 1947–55.	3,310 Population sample approximately proportional to cases as regards areas of residence, and 10 years or more in the area.	Cases: From death certificates, hospital records, and close relatives or friends. Controls: Personal home visits or telephone calls, usually interviewing housewife.
Stocks 1957 (335)	England	M–F	2,356 Patients suffering from or dying with lung cancer within certain areas.	9,362 Unselected patients of the same area admitted for conditions other than cancer.	Cases: Histories taken at the hospital or from relatives by health visitors. Controls: Personal interview in hospital.

TABLE 2.—*Outline of methods used in retrospective studies of smoking in relation to lung cancer*—Continued

Investigator, year, and reference	Country	Sex of cases	Number of persons and method of selection		Collection of data
			Cases	Controls	
Schwartz and Denoix 1957 (313).	France	M	602 Patients with bronchopulmonary cancer in hospitals in Paris and a few other cities.	1,204; 3 groups: patients in same hospitals with other cancer, with non-cancer illness, and accident cases, matched by age group.	Personal interviews in the hospital; cases and controls at about the same time by the same interviewer.
Haenszel et al., 1958 (150)	U.S.A.	F	158 Lung cancer patients available for interview in 29 hospitals, 1955–57.	339 Patients in same hospital and service at same time, next older and next younger than each case.	Personal interviews by resident, medical social worker, or clinic secretary.
Lombard and Snegireff 1959 (222).	U.S.A.	M	500 Men dying of lung cancer, microscopically confirmed, 1952–53.	4,238 Controls in 7 groups including volunteers, hospital and clinic patients, random population sample, and house-to-house survey samples.	Personal interviews by trained workers.
Pernu 1960 (277)	Finland	M–F	1,606 Respiratory cancer patients in 4 hospitals and from cancer registry between 1944 and 1958.	1,773 Cancer-free persons recruited by Parish Sisters of 2 institutes in all parts of the country.	Cases: From case histories or mailed questionnaires. Controls: Questionnaires distributed by Parish Sisters.
Haenszel et al., 1962 (147)	U.S.A.	M	2,191 Sample of 10 percent of white male lung cancer deaths in the U.S. in 1958.	31,516 Random sample from Current Population Survey used to estimate population base.	Cases: By mail from certifying physicians and family informants. Population: Personal interview by Census enumerators.
Lancaster 1962 (199)	Australia	M	238 Hospital patients with lung cancer	476 Two groups, one with other cancer, one with some other disease, matched by sex and age.	Personal interviews of both cases and controls in hospitals.
Haenszel and Taeuber 1963 [1] (152).	U.S.A.	F	749 Sample of 10 percent of white female lung cancer deaths in the U.S. in 1958 and 1959.	34,339 Random sample from Current Population Survey used to estimate population base.	Cases: By mail from certifying physicians and family informants. Population: Personal interview by Census enumerators.

[1] To be published.

Germane to this concordance is a recent study (386) of Seventh Day Adventists, a religious group in which smoking and alcohol consumption are uncommon. On the basis of expectancy of male lung cancer incidence derived from the control population, only 10 percent of the cases expected were actually found among Seventh Day Adventists.

FORM OF TOBACCO USE

In considering the details of the individual retrospective studies listed in Tables 2 and 3, 13 of the studies, combining all forms of tobacco consumption, found a significant association between smoking of any type and lung cancer (138, 199, 211, 250, 277, 280, 283, 309, 316, 363, 365, 379, 381); 16 studies yielded an even stronger association with cigarettes alone as compared to pipe and/or cigar smoking (38, 82, 147, 192, 207, 222, 236, 237, 238, 277, 283, 301, 311, 314, 335, 379) when these forms of smoking were considered separately and in combinations for males. The females, in the studies investigating the relationship of smoking and lung cancer among them, were almost invariably cigarette smokers so that comparisons with other forms of tobacco use were not indicated.

AMOUNT SMOKED

Twenty-six of the studies quantitated the amount of smoking per day either by combining weights of tobacco consumed in any form, or, more often, by quantities of the specific forms of tobacco. In each of the studies investigating male lung cancer, the degree of association increased as the amount of smoking increased (38, 82, 138, 147, 150, 192, 199, 211, 222, 236, 250, 277, 280, 283, 301, 309, 311, 314, 316, 335, 363, 365, 379, 381). One retrospective study (82) by Doll and Hill found a sharper difference in amount smoked between cases and controls among recent smokers (10 years preceding onset of the disease) than in a comparison of the maximum amount ever smoked. The authors cautioned against accepting this finding as being against their hypothesis of a gradient of risk (which would more properly be tested by the whole life history of "exposure to risk") by citing the inaccuracies resulting from "requiring the patient to remember habits of many years past."

Of the 11 retrospective studies with data on females and tobacco use by amount smoked daily, six (211, 236, 277, 283, 365, 381) showed trends of increasing association with amount smoked daily, but had too few cases for reliability of the trend. However, five studies (82, 150, 152, 335, 375) did have large numbers of female lung cancer cases for analysis by smoking class; three of these (150, 152, 375) were directed towards female cases only. In each of these latter five studies, the degree of association increased with the amount of cigarettes smoked daily.

Four of the retrospective studies dealt with *ex-smokers* as well (147, 152, 211, 314); in one of these (314), where relative risks were derived indirectly by the Cornfield method (61), and in another by conventional use of standardized mortality ratios (147), male ex-smokers showed a lower risk than

TABLE 3.—*Group characteristics in retrospective studies on lung cancer and tobacco use*

Authors	Reference	Year	Males						Females						Remarks
			Cases			Controls			Cases			Controls			
			Number	Percent non-smokers	Percent heavy smokers [1]	Number	Percent non-smokers	Percent heavy smokers [1]	Number	Percent non-smokers	Percent heavy smokers [1]	Number	Percent non-smokers	Percent heavy smokers [1]	
Müller	(250)	1939	86	3.5	65.1	86	16.3	36.0	(*)	(*)	(*)	(*)	(*)	(*)	
Schairer & Schoeniger	(309)	1943	93	3.2	31.2	270	15.9	9.3	(*)	(*)	(*)	(*)	(*)	(*)	16 female cases not analyzed.
Potter & Tully	(280)	1945	43	7.0	30.2	1,847	26.0	23.0	(*)	(*)	(*)	(*)	(*)	(*)	
Wassink	(363)	1948	134	4.8	54.8	100	19.2	19.2	(*)	(*)	(*)	(*)	(*)	(*)	Percentages estimated from chart.
Schrek et al	(311)	1950	82	14.6	18.3	522	23.9	9.2	(*)	(*)	(*)	(*)	(*)	(*)	
Mills & Porter	(237)	1950	444	7.2	(**)	430	30.5	(**)	(*)	(*)	(*)	(*)	(*)	(*)	
Levin et al	(207)	1950	236	15.3	(**)	481	21.7	(**)	(*)	(*)	(*)	(*)	(*)	(*)	Quantity smoked not considered.
Wynder & Graham	(381)	1950	605	1.3	51.2	780	14.6	19.1	40	57.5	25.0	552	79.6	1.2	
McConnell et al	(236)	1952	93	5.4	38.5	186	6.5	23.2	7	57.1	(**)	14	78.6	(**)	
Doll & Hill	(82)	1952	1,357	0.5	25.1	1,357	4.5	13.4	108	37.0	11.1	108	54.6	0.9	Percentage "heavy" smokers understated.
Sadowsky et al	(301)	1953	477	3.8	(**)	615	13.2	(**)	(*)	(*)	(*)	(*)	(*)	(*)	Gradient with amount smoked.
Wynder & Cornfield	(379)	1953	63	4.1	67.6	133	20.6	29.3	(*)	(*)	(*)	(*)	(2)	(*)	
Koulumies	(192)	1953	812	0.6	58.9	300	18.0	25.0	(**)	(**)	(**)	(*)	(*)	(*)	
Lickint	(211)	1953	224	1.8	35.8	1,000	16.0	4.8	22	64.0	4.5	1,002	90.4	0.1	
Breslow et al	(38)	1954	518	3.7	74.1	518	10.8	42.7	(**)	(**)	(**)	(**)	(**)	(**)	Data include 493 males, 25 females.
Watson & Conte	(365)	1954	265	1.9	71.7	287	9.7	51.6	36	58.3	2.8	181	82.0	1.1	
Gsell	(138)	1954	135	0.7	68.1	135	16.0	14.0	(*)	(*)	(*)	(*)	(*)	(*)	
Randig	(283)	1954	415	1.2	34.2	381	5.8	17.9	33	51.5	3.0	131	70.3	0	
Stocks & Campbell	(337)	1955	(See reference (335) below)												
Wynder et al	(375)	1956	(*)	(*)	(*)	(*)	(*)	(*)	105	56.2	16.2	1,304	66.0	3.4	
Segi et al	(316)	1957	166	(**)	(**)	2,124	(**)	(**)	(**)	(**)	(**)	(**)	(**)	(**)	Quantities smoked stated as averages only. Differences are statistically significant.
Mills & Porter	(238)	1957	484	8.4	26.0	1,588	27.6	5.3	94	83.0	4.3	1,722	73.3	0.5	Percent "heavy" smokers understated. Only 50% survey response among female cases.
Stocks	(335)	1957	2,101	1.9	28.2	5,960	8.7	22.3	255	57.6	17.2	3,402	68.6	10.7	
Schwartz & Denoix	(313)	1957	602	1	58.2	1,204	9.5	36.2	(*)	(*)	(*)	(*)	(*)	(*)	
Haenszel et al	(150)	1958	(*)	(*)	(*)	(*)	(*)	(*)	158	51.9	14.6	339	69.6	8.2	

Lombard & Snegireff	(222)	1959	500	1.6	(**)	4,238	11.0	(**)	(*)	(*)	(*)	(*)	(*)	(*)	Authors' calculations for heavy smoking based on lifetime number of packs of cigarettes.
Pernu	(277)	1960	1,477	6.6	34.5	713	37.2	20.8	129	85.3	26.4	1,060	91.6	0.7	Quantities given only in grams per day.
Haenszel et al	(147)	1962	2,191	3.4	41.9	(*)	16.2	12.0	(*)	(*)	(*)	(*)	(*)	(*)	Population sample of 31,516 used as base. Not a case-control study.
Lancaster	(199)	1962	238	2.5	86.1	476	20.1	71.2	(*)	(*)	(*)	(*)	(*)	(*)	
Haenszel & Taeuber	(152)	[2]1963	(*)	(*)	(*)	(*)	(*)	(*)	749	60.9	11.5	(2)	67.3	2.5	Population sample of 34,339 used as base. Not a case-control study.

[1] For this table heavy smokers are defined as those smoking 20 or more cigarettes per day.
[2] To be published.
*Does not apply.
**Data not given.

current smokers but greater than non-smokers. In a third study (152) of lung cancer in women, the ex-smoker risk was lower than the current-smoker risk but approximately equal to that for the non-smoker.

DURATION OF SMOKING

Duration of smoking, was considered in 12 of the retrospective studies (82, 150, 207, 222, 236, 283, 301, 311, 316, 335, 375, 381). In only six of them, however, were the data treated in such a way as to permit evaluation of the relationship between duration of smoking and lung cancer–two studies in males (207, 301) ; two in males and females (82, 236) ; and two in females only (150, 375). Among the studies of male lung cancer, Levin (207), correcting his data for age, found a relationship between the number of years of cigarette smoking and lung cancer. McConnell (236) found a significant difference in duration of smoking between cases and controls, but was reluctant to draw any definite conclusions. On the other hand, Doll and Hill (82), in their age- and sex-matched study, showed a distinct and statistically significant association between the duration of smoking among males. In a well-conceived analytic study, Sadowsky et al. (301), recognizing that duration of smoking is a function of age, controlled the age variable, and found an increasing prevalence rate of lung cancer with an increase in duration of smoking among all age groups (age at diagnosis).

Among the studies including data on female lung cancer, McConnell had too few female cases to resolve the question of duration of smoking (236) and Doll and Hill, though finding differences between cases and controls. could not establish statistical significance (82). In the two investigations in which only female lung cancer cases were studied (150, 375), neither showed an independent association between duration of smoking and lung cancer. Haenszel states, however, that "among women, the association of starting age and duration of tobacco use with current rate is so strong that it may be unrealistic to expect to find a separate duration effect in retrospective studies of limited size" (150).

AGE STARTED SMOKING

Closely related to duration of smoking and thus pertinent to the length of time that subjects have been exposed to tobacco smoke is the variable of age when smoking was started. Relatively few of the retrospective studies have dealt with this variable. Koulumies (192) found that males with lung cancer had started smoking significantly earlier in life In fact, 143 of his 845 cases or 17 percent began to smoke below 10 years of age as compared to 6.5 percent among his matched controls. The study of male cases and controls by Breslow et al. (38) found a definite trend in the same direction. Pernu (277) found a statistically significant difference in age at start of smoking, with a higher proportion of the male lung cancer group starting at under 15 years of age. Lancaster (199) indicated that the male lung cancer patients began to smoke at a significantly younger age. One other study (283) showed no difference.

Of the three investigations of female lung cancer which explored this variable, there were too few smokers in one study for a test of significance (277), and in the remaining two (150, 283), no differences were found.

INHALATION

If the association between smoking, particularly cigarette smoking, and lung cancer is a causal relationship, then inhalation should provide more exposure than non-inhalation and should thus contribute significantly to the lung cancer load. Four retrospective investigations were addressed to this question. In the earlier Doll and Hill study (82), no difference in the proportion of smokers inhaling was found among male and female cases and controls. However, four subsequent studies of men (38, 211, 222, 313) found inhalation of cigarettes significantly associated with lung cancer. Although in Breslow's study (38) of age-, sex- and race-matched case and control patients, the variable "quantity-smoked" was not held constant in the comparison when type of smoking though not quantity was controlled, an association was found between inhalation and lung cancer. In the study by Schwartz and Denoix (313) who held constant both type of smoking and amount of cigarettes smoked, the relationship of inhalation was significant for those smoking cigarettes alone but not for the smokers of both cigarettes and pipes. Furthermore, although inhalers among lung cancer patients averaged a significantly higher number of cigarettes per day than did the controls, the relative risk differences between inhalers and non-inhalers, calculated by the Cornfield method (61), become smaller and almost equal each other at the highest cigarette consumption levels. Lombard and Snegireff (222) demonstrated similar relative risk ratios.

HISTOLOGIC TYPE

The earliest retrospective study which considered histologic type of lung cancer was by Wynder and Graham (381) in 1950. These authors presented data on smoking habits of male and female adenocarcinomatous patients and for female patients with epidermoid cancers which were but 25 in number. With this partial analysis only a hint of a higher proportion of smokers among female epidermoid cases could he derived. Of the 1,465 lung cancers in the Doll and Hill retrospective study (82), 995 were histologically confirmed (916 males and 79 females). Of the confirmed cases, 85 percent of the males and 71 percent of the females were of the epidermoid or anaplastic type. Although no statistically significant difference in smoking habits was elicited for the several types, a relatively higher proportion of non-smokers and light smokers were found among patients of both sexes with adenocarcinoma.

Following the presentation by Kreyberg of a Typing Classification of the epidermoid and oat cell or anaplastic types as Group I and the adenocarcinoma and bronchiolar or alveolar cell types as Group II, and the suggestion of a relationship between Group I and smoking (196), several ensuing retrospective studies dealt with this question.

Breslow's study revealed a higher percentage of non-smokers among the patients with adenocarcinoma than among those with epidermoid types (38). In rapid succession six additional retrospective studies analyzed the relationship between histologic type of lung cancer and smoking. The 1956 study of female lung cancers by Wynder et al. (375) indicated that adenocarcinomata apparently had little or no relationship to smoking but that a relationship did exist between smoking and the epidermoid and anaplastic types. Schwartz et al. (313), similarly, in 1957, found a highly significant

association between smoking of cigarettes, amount of smoking as well as inhaling, and the epidermoid and anaplastic types of tumors. No such association with "type cylindrique" was noted. In that same year Doll and Hill furnished Kreyberg with lung cancer slides from 933 British patients. Kreyberg, without knowledge of the patients' smoking history or clinical data, separated these into two groups. A strong correlation was found between smoking history and histologic type; smoking and amount were highly associated with the epidermoid and anaplastic types, and non-smokers were predominantly among the adenocarcinomatous types (86).

In this study of lung cancer in women, Haenszel, et al. (150) found statistically significant relative risk gradients for amount of cigarette smoking among Group I cancer patients. No increased risk was established for Group II cancers. In his later studyof a current mortality sample of white males for 1958, Haenszel found relative risk gradients for the several smoking classes for both adenocarcinomas and epidermoid cancers (147). A parallel study of white females for the current mortality sample of 1958 and 1959 showed essentially the same findings, except possibly for a lower effect on adenocarcinomas among smokers of less than one pack daily (152).

Haenszel points out that in both these studies a "true differential in risks" for the two histologic types could well have been diluted seriously by reporting and classification errors which were definitely known to exist from reinquiry of a sub-sample of deaths (152). (For current evaluation, see section on Typing of Lung Tumors.)

RELATIVE RISK RATIOS FROM RETROSPECTIVE STUDIES

Retrospective studies are usually designed to establish the probability of association of an attribute A with disease X; or, given disease X, what is the probability that A will be found in association (P [A | X])? Procedurally, one compares a supposedly representative group of patients with disease X, with another group as controls, in regard to the percentages of individuals with and without the attribute A. This procedure may reveal significant differences leading to judgments of association but it does not yield an estimate of the magnitude of the relative risk of disease X among those with attribute A and those without. A method which estimates this relative risk, developed by Cornfield (61), has been referred to several times earlier and can be applied to data derived from retrospective studies if two assumptions, inherent in the first procedure of judging the association, are made: (a) that patients with disease X interviewed or otherwise studied are a representative sample of all cases with disease X, and (b) that the controls without disease X or who have escaped disease X are a representative sample of all persons without disease X. An estimate of the prevalence of disease X in the population is a requisite.

Such an approach was utilized by a number of investigators in retrospective studies on lung cancer. Doll and Hill (82) made similar calculations and found a linear gradient of deaths from lung cancer for men and women increasing with amount of tobacco smoked daily. Sadowsky et al. (301) found similar increases in risk for amount smoked daily in virtually all but the oldest age groups and calculated an age-standardized risk ratio of 4.6:1 for all smokers compared to non-smokers. These authors also

utilized the data of Wynder and Graham (381) and Doll and Hill (82) for calculating similar risk ratios, deriving ratios of 13.6:1 and 13.8:1, respectively. Their calculations of estimated prevalences by quantity smoked daily for age groupings similar to their own also showed linear increases of risk.

Breslow et al. (38) treated their retrospective data similarly and developed relative risk ratios of 7.7:1 for males aged 50-59 years and 4.6:1 for those aged 60-69. In considering heavy smokers (40 or more cigarettes per day), they showed relative risk ratios of 17:1 and 25.5:1, respectively. Randig (283) also demonstrated a linear progression of risk with increasing amounts of daily tobacco consumption and an over-all ratio of 5.1:1 for all smokers to non-smokers among males and 2.2:1 for females. Schwartz and Denoix (313) reported similar findings in amount smoked daily and a risk ratio of smokers to non-smokers of approximately 8:1. Lombard and Snegireff (222) approached their data in a different way, utilizing "lifetime number of packs of cigarettes consumed" as a measure of exposure. Their estimated prevalence rates also increase linearly with amount smoked. The risk ratio which can be calculated from their tabulated data ranges from 2.4:1 for light smokers to 34.1:1 for heaviest smokers.

Haenszel, in his two studies on male and female lung cancer mortality as related to residence and smoking histories, calculated relative risk ratios of 4.1:1 for one pack or less daily and 16.6:1 for more than one pack a day among males (147), and 2.5:1 and 10.8:1, respectively, among females (152). Table 4 summarizes the relative risk findings of the nine studies.

Prospective Studies

It has been pointed out that in retrospective studies the usual approach is to determine the frequency of an attribute among cases and controls. This measure does not provide estimates of the risks of developing the disease

TABLE 4.—*Relative risks of lung cancer for smokers from retrospective studies*

Author and Reference	Year	Sex	Relative risk—Smokers: non-smokers
Sadowsky et al (301)	1953	M	4.6
Doll and Hill (82)	1952	M	13.8
Wynder and Graham (381)	1950 [1]	M	13.6
Breslow et al. (38)	1954	M	7.7 age 50–59 4.6 " 60–69 17.0 " 50–59 } very heavy smokers 25.5 " 60–69 }
Randig (283)	1954	M–F	5.1 M 2.2 F
Schwartz and Denoix (313)	1957	M	8.0
Lombard and Snegireff (222)	1959	M	2.4 light smokers 3.1 heavy smokers
Haenszel (147)	1962	M	4.1 <1 pack/day 16.6 >1 pack/day
Haenszel (152)	Unpublished	F	2.5 <1 pack/day 10.8 >1 pack/day

[1] Calculated by Sadowsky et al. (301) from other authors' data.

among individuals with and without the attribute unless one makes assumptions referred to above. The validity of such assumptions may at times be suspect, for the cases may not be representative of the total population with the disease nor the controls representative of the population without the disease. Thus, some retrospective studies may not truly assess the existent risks with reasonable accuracy. However, when *all* the cases of a disease in an area and a representative sample of the population without the disease are included in a study, the estimates of risk bear high validity.

Despite the criticisms leveled at the retrospective method in general and its obvious defects as practiced by some investigators, a number of the retrospective studies on lung cancer have indeed overcome most of the criticisms of major import leveled at the method. These criticisms and their implications will be treated specifically below in the section on an Evaluation of the Association Between Smoking and Lung Cancer. Suffice it to say at this point that certain shortcomings of the retrospective survey approach, some real and some exaggerated, led several courageous investigators to undertake the necessarily protracted, expensive, and difficult prospective approach.

The first prospective study encompassing total and cause-specific mortality in a human population was initiated in October 1951 among British physicians by Doll and Hill (83, 84). There then followed in rather rapid succession, five additional independent studies in the United States and Canada (25, 87, 88, 96, 97, 157, 162, 163), all but one of which continue to be active. The earlier study, by Hammond and Horn, among 187,783 white males aged 50-69 years, initiated between January and May 1952, was terminated after 44 months of follow-up (162, 163). This has been succeeded by the current Hammond study which broadened its age-base (35–89 years) and contains 1,085,000 persons (in 25 states) of whom 447,831 are males (157).

These studies have been described in detail, analyzed, and evaluated in Chapter 8 of this Report where a discussion of differences in total mortality between smokers and non-smokers has been presented, and are summarized in Table 1 of that chapter. All the prospective studies thus far have shown a remarkable consistency in the significantly elevated mortality ratios of smokers particularly among the "cigarettes only" smoking class. Of special interest is the fact that in a number of the studies the magnitude of the association between cigarette smoking and total death rates has increased as the studies have progressed. This has particularly been true for lung cancer. The presently calculated total mortality ratios have been presented in Table 2 of Chapter 8 of this Report.

With reference to the smoking and lung cancer relationship, each of the seven prospective studies has thus far revealed an impressively high lung cancer mortality ratio for smokers to non-smokers. Examination of Table 5, which presents in summary form the lung cancer mortality ratios for the seven studies by smoking type and amount, derived both from the published reports of these studies and current information from the investigators wherever available, reveals a range of ratios from 6.0 to 25.2 with a median value of 10.7 for all smokers irrespective of type or amount. For smokers currently using cigarettes only at the time of enrollment in the studies, the ratios range from 4.9 to 20.2 with a mean value of 10.4 as derived from a summation of observed and expected values of most recent data.

Several of the studies have fortunately provided data for a measure of the "dose of exposure" relationship (84, 88, 96, 157, 163). It can readily be seen from Table 5 that the mortality ratios increase progressively with amount of smoking. The pivot level appears to be 20 cigarettes per day. Cigar and/or pipe smokers (to the exclusion of cigarettes) manifest ratios lower than any of the cigarette smoking classes, including combinations of cigarettes with pipes and/or cigars (25, 84, 88, 157, 163). One study provided data on occasional smokers (163). These have a ratio very close to that of non-smokers. Ex-smokers of cigarettes (83, 88, 163) fall into levels of risk ratios below those for current smokers of cigarettes depending upon the length of the interval since smoking was stopped. In the Doll and Hill study (83), the ex-smoker ratio was less than the current smoker ratio even when cessation had occurred less than 10 years before entry into the study. This, however, was not true for the first Hammond and Horn study (163). In this latter study, if smoking had ceased more than 10 years before entry, the lung cancer mortality ratios were lower than for current smokers at the corresponding daily consumption levels, but if cessation of smoking had occurred less than 10 years before entry, the ratios were virtually identical to those for current cigarette smokers at the corresponding daily consumption levels. The Dorn material (87, 88), currently brought up to date (89), provides a measure of relative risk by amounts of smoking prior to stopping. The ratios thus elicited are again below those for current cigarette smokers of corresponding daily amounts.

At this time it is difficult to assess the effect of other variables such as duration of smoking and starting age on lung cancer mortality since cross-classification by these variables, and amount smoked as well, leads to cells with small numbers of deaths. Most prospective studies have thus far confined themselves to analyzing the effect of these additional variables on deaths from all causes, or in one case (157) from cardiovascular diseases. The current Hammond study is concerned with inhalation practices, but here also the total number of lung cancer deaths analyzed to date does not permit extensive classification by age, type of smoking, amount smoked daily, present smoking status, and age when smoking was begun. In the studies of total mortality ratios, duration of smoking, obviously immediately dependent upon the age of the individual, was in turn dependent upon age when smoking (cigarettes) was begun. Age when smoking began was also a determinant, not only of the number of cigarettes smoked daily, but of the degree of inhalation, with smokers starting at earlier ages very distinctly tending to smoke more and inhale more deeply than those starting to smoke at older ages (157). According to Hammond, men who smoke more per day also tended to inhale more deeply than those who smoke fewer cigarettes per day. When inhalation and quantity smoked were held constant, the total mortality ratios also increased as age at start of smoking decreased.

The stability of the lung cancer mortality ratios referred to in Table 5 is to a great extent dependent upon the number of observed lung cancer deaths among non-smokers from which the expected values for the several smoker classes are calculated, Referring again to Table 5, in at least two of the studies (83, 96), calculation of the expected deaths among smoker classes had to be based on extremely small numbers of non-smokers. However,

TABLE 5.—*Mortality ratios for lung cancer by smoking status, type of smoking, and amount smoked, from seven prospective studies*

Study	Doll and Hill	Hammond and Horn	Dorn	Dunn, Linden and Breslow—Occupational	Dunn, Buell and Breslow—Legion	Best, Josie and Walker	Hammond
Lung cancer deaths in Study	129	448	535	139	98	221	414
Lung cancer deaths Non-smokers	†3	†25	†56	†3	†12	†8	†16
(Reference number)	(83)	(163)	(88)	(96)	(97)	(25)	(157)
MORTALITY RATIOS:							
All Smokers	12 8	10. 7	6.0	–	–	*25 2	†8. 1
1–14 gm. tobacco	6. 7	–	–	–	–	–	–
15–24 gm. tobacco	12 3	–	–	–	–	–	–
25 gm. tobacco	23. 7	–	–	–	–	–	–
Current. **							
Cigarettes only	†20. 2	†10. 0	†12. 0	†15. 9	†4. 9	†11. 7	†9 6
<10	4. 4	†5. 8	†5. 2	(5)– 8. 3	–	†8 4	–
10–20	10. 8	†7. 3	†9. 4	(10)– 9. 0	–	†13. 5	–
21–39	43. 7	†15. 9	†18 1	(20)–19 4	–	†15 1	–
40+		†21. 7	†23. 3	(30)–25. 1	–		–
				(40)–28 7			
≦1 pack †	8. 1	6. 9	8. 1	13 6	4 2	11. 8	–
>1 pack †	43. 8	16 9	18. 0	24. 1	7. 4	15 1	–
Pipes only	5. 4	2. 6	1 3	–	–	†1. 1	†1 5
Cigars only	†4. 6	1. 0 †1. 3	1. 5 †1. 6	–	–		
Pipes and cigars		–	–	–	–		
Cigarettes, pipes and cigars	9. 7	10. 7	6. 2	–	–	†24. 4	–
Occasional	–	1. 3	–	–	–	–	–
Ex-Smokers:							
>10 yrs. since stopped	5. 0	–	–	–	–	–	–
<20 cigarettes	–	2. 4	–	–	–	–	–
>20 cigarettes	–	17. 8	–	–	–	–	–
<10 yrs. since stopped	8. 4	–	–	–	–	–	–
<20 cigarettes	–	10. 4	–	–	–	–	–
>20 cigarettes	–	22. 8	–	–	–	–	–
<20 cigarettes (irrespective of when stopped)	–	–	†1. 3	–	–	–	–
>20 cigarettes (irrespective of when stopped)	–	–	†1. 6	–	–	–	–

*Current and ex-smokers combined.
†Most recent information.
–Data not available or not available for designated classes.
**Two California studies and current Hammond study include all cigarette smokers (cigarettes and other and current and ex-cigarette smokers)

the other studies have now yielded significantly greater numbers of non-smoker lung cancer deaths and in at least three of them (88, 157, 163) these are now appreciable.

Experimental Pulmonary Carcinogenesis

ATTEMPTS TO INDUCE LUNG CANCER WITH TOBACCO AND TOBACCO SMOKE

Few attempts have been made to produce bronchogenic carcinoma in experimental animals with tobacco extracts, smoke, or smoke condensates. With one possible exception (289), none has been successful (331).

Mice rarely develop spontaneous bronchogenic, oral, esophageal, gastric, prostatic, laryngeal, or vesical carcinomas, but certain inbred strains have a high incidence of spontaneous pulmonary adenomas (6). The administration, by any route, of carcinogenic polycyclic hydrocarbons, including some found in tobacco tar, increases the incidence and decreases the time of occurrence of pulmonary adenomas. These tumors arc usually regarded as benign, and probably arise from the alveolar epithelium (4, 5, 6, 131, 330) rather than the bronchial wall. They have no resemblance to most human bronchogenic carcinomas.

Essenberg (106) and Muhlbock (248) exposed mice to cigarette smoke, but their reported results are equivocal. Lorenz et al. (224) and Leuchtenberger et al. (206) did not observe an increase in pulmonary adenomas in mice that inhaled cigarette smoke.

Leuchtenberger et al. (205a.) described a sequence of microscopic changes in lungs of mice exposed to cigarette smoke resembling somewhat those found by Auerbach et al. in the lungs of human smokers. No dose-response effect was reported. The morphologic findings consisted of bronchitis with proliferation of the epithelium. Some areas of hyperplasia showed atypical changes. However, the changes were reversible when exposure to smoke was stopped. The production of bronchogenic carcinomas has not been reported by any investigator exposing experimental animals to tobacco smoke.

Most experiments in which tobacco tars were brought into direct contact with the lung and tracheabronchial tree of experimental animals have yielded negative results (273, 274, 275). Blacklock (29) found one carcinoma when tar from cigarette filters was placed in olive oil together with killed tubercle bacilli and injected into the hilum of a small number of rats. Rockey et al. (289) painted tobacco tar three to five times each week on the trachea of dogs with a tracheacutaneous fistula. Hyperplastic changes with squamous metaplasia of the bronchial epithelium were seen in seven dogs that survived 178 to 320 days. Carcinoma-in-situ was reported to occur in three, and invasive carcinoma in one out of 137 dogs, but this work has not yet been confirmed.

SUMMARY.--Bronchogenic carcinoma has not been produced by the application of tobacco extracts, smoke, or condensates to the lung or the tracheobronchial tree of experimental animals with the possible exception of dogs.

SUSCEPTIBILITY OF LUNG OF LABORATORY ANIMALS TO CARCINOGENS

POLYCYCLIC AROMATIC HYDROCARBONS.—Epidermoid carcinoma has been induced in mice by Andervont by the transfixion of the lungs or bronchi with a thread coated with a carcinogen (5) and by Kotin and Wiseley (191) by treatment with an aerosol of ozonized gasoline plus mouse-adapted influenza viruses.

Kuschner et al. (197, 197a) induced epidermoid carcinomas in the lungs of rats by the local application of polycyclic aromatic hydrocarbons, either by thread transfixation or pellet implantation. Distant metastases occurred from some of the carcinomas. The changes in the bronchial tree at different times prior to the appearance of cancer included hyperplasia, metaplasia and anaplasia of the surface epithelium as well as of the subjacent glands. These changes resembled those described by Auerbach in the tracheobronchial tree of human smokers (9).

Stanton and Blackwell (324) induced epidermoid carcinoma in the lungs of rats that had received 3-methylcholanthrene intravenously. The carrinogen was deposited in areas of pulmonary infarction.

Saffiotti et al. (302) produced squamous cell bronchogenic carcinomas in hamsters by weekly intubation and insufflation of benzo(a)pyrene (4 percent) ground with iron oxide (96 percent) resulting in a dust with particles smaller than 1.0 micron.A proliferative response followed by metaplasia preceded the appearance of the carcinomas, but was not an invariable antecedent.

VIRUSES.—Bronchogenic carcinoma has been induced in animals inoculated with polyoma virus by Rabson et al. (282). Carcinogens enhance the effect of viruses known to cause cancer in animals (99) and localize the neoplastic lesions at the site of inoculation of the virus (98). However, no evidence has been forthcoming to date implicating a virus in the etiology of cancer in man.

POSSIBLE INDUSTRIAL CARCINOGENS.—Vorwald reported that exposure of rats to beryllium sulfate aerosol resulted in carcinomas of the lung; 12 percent were epidermoid but most were adenocarcinomas. The tumors usually arose from the alveolar or bronchiolar epithelium. He also produced bronchogenic carcinomas in two out of ten rhesus monkeys injected with beryllium oxide and in three out of ten exposed to beryllium oxide by inhalation (357).

Lisco and Finkel in 1949 (217) reported the production of epidermoid cancer of the lung in rats with radioactive cerium. Subsequently many other investigators have succeeded in producing carcinomas of the lung, predominantly of the epidermoid type, in a high percentage of rats and mice with other radioactive substances. The various modes of exposure included inhalation, intratracheal injection, or insufflation and implantation of wire or cylinder. These experiments were reviewed by Gates and Warren in 1961 (125).

Huerper exposed rats and guinea pigs to nickel dust and found metaplastic and anaplastic changes in the bronchi (180). Following up earlier work in which squamous metaplasia of the bronchial epithelium was found in rats exposed to nickel carbonyl (341). Sunderman and Sunderman (342) induced bronchogenic carcinoma in rats by exposure to this compound. This

group also found 1.59 to 3.07 μg. of nickel per cigarette in the ash and in the smoke in several different brands. About three-fourths was contained in the ash. Although Huerper and Payne (182, 183) and Payne (270) have demonstrated that pure chromium compounds will produce both sarcomas and carcinomas in several tissues in rats and mice, bronchogenic carcinomas have not been produced by inhalation of chromium compounds in experimental animals. Experiments designed to test the carcinogenicity of arsenical compounds have been either negative or inconclusive.

Asbestosis can be produced without difficulty in experimental animals by inhalation of asbestos fibers (359), but efforts to produce bronchogenic carcinoma have been unsuccessful (129, 181, 227, 358).

SUMMARY.—The lungs of mice, rats, hamsters, and primates have been found to be susceptible to the induction of bronchogenic carcinoma by the administration of polycyclic aromatic hydrocarbons, certain metals, radioactive substances, and oncogenic viruses. The histopathologic characteristics of the tumors produced are similar to those observed in man and are frequently of the squamous variety.

ROLE OF GENETIC FACTORS IN PULMONARY ADENOMAS IN MICE

Genetic factors exert a determining influence on the spontaneous development and induction of Iung tumors in mice. Early studies of Murphy and Sturm (251) and of Lynch (225, 226) demonstrated the development of pulmonary tumors in mice after the skin was painted with coal tar, and Lynch (225) indicated the existence of genetic factors in the development of these tumors. Later investigations of Heston (169, 170) on the effect of intravenous injection of dibenzanthracene and the studies of several other investigators (3, 4, 27, 47, 320) utilizing different techniques gave additional evidence of the operation of genetic factors in induced tumors. Linkage between multiple genes for susceptibility to spontaneous and induced tumors in mice and specific chromosomes has also been established (47, 168) and transplantation experiments (171, 173) indicate that the genetic susceptibility resides within the pulmonary parenchyma. A number of investigators (36, 47, 124, 131) demonstrated conclusively that these tumors usually arise distal to the bronchus and are probably alveogenic. Metastases rarely occur. The relative importance of genes for susceptibility to these tumors of the lung is indicated by an incidence ranging from a few tumors to over 90 percent, depending on the inbred strain examined.

Spontaneous tumors of the lungs are rare in species of laboratory animals other than mice, and the genetics of these neoplasms in other species has been investigated only superficially.

SUMMARY.—Genetic susceptibility plays a significant role in the development of pulmonary adenomas in mice.

Pathology — Morphology

RELATIONSHIP OF SMOKING TO HISTOPATHOLOGICAL CHANGES IN THE TRACHEOBRONCHIAL TREE

In an extensive and controlled blind study of the tracheobronchial tree of 402 male patients, Auerbach et al. (11, 13, 15) observed that several

kinds of changes of the epithelium were much more common in the trachea and bronchi of cigarette smokers and subjects with lung cancer than of non-smokers and of patients without lung cancer (Table 6). The epithelial changes observed were (a) loss of cilia, (b) basal cell hyperplasia (more than two layers of basal cells), and (c) presence of atypical cells. The atypical cells had hyperchromatic nuclei which varied in size and shape. The arrangement of such cells was frequently disorderly (see illustrations below). Hyperplastic changes were also seen in the bronchial glands.

TABLE 6. *--Percent of slides with selected lesions,[1] by smoking status and presence of lung cancer*

Group	Number cases	Number slides	Percent of slides with cilia absent and averaging 4 or more cell rows in depth			
			No cells atypical	Some cells atypical	All cells atypical [2]	Total
Cases without lung cancer						
Never smoked regularly	65	3,324	1.0		0.03	**1.1**
Ex-cigarette smokers		3,436	3.5	0.4	0.2	**4.1**
Cigarettes--1/2 pk. a day	72	1,824	0.2	4.2	0.3	**4.7**
Cigarettes--1/2-1 pk. a day	59	3,016		7.1	0.8	7.9
Cigarettes--1-2 pks. a day	143	7,062		12.6	4.3	16.9
Cigarettes--2+ pks. a day	36	1,787		26.2	11.4	37.5
Lung cancer cases [3]	63	2,784		12.5	14.3	26.8

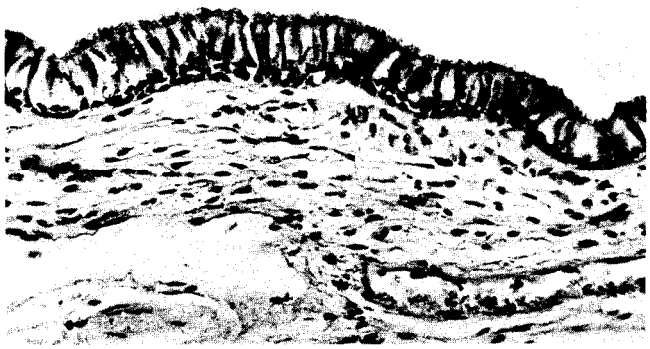
[1] In some sections, two or more lesions were found. In such instances, all of the lesions were counted and are included in both individual columns and in the total column of the table. Lesions found at the edge of an ulcer were excluded.

[2] These lesions may be called carcinoma-in-situ.

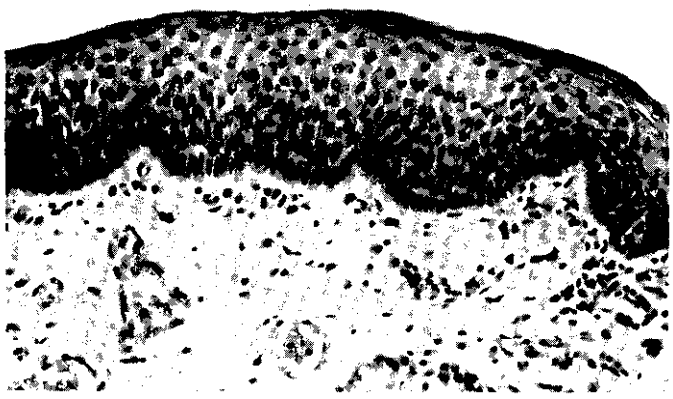
[3] Of the 63 who died of lung cancer, 55 regularly smoked cigarettes up to the time of diagnosis, 5 regularly smoked cigarettes but stopped before diagnosis, 1 smoked cigars, 1 smoked pipe and cigars, 1 was an occasional cigar smoker.

Each of the three kinds of epithelial changes was found to increase with the number of cigarettes smoked (Table 6). In smokers who had no cancers, frequency and intensity of these changes correlated with the number of

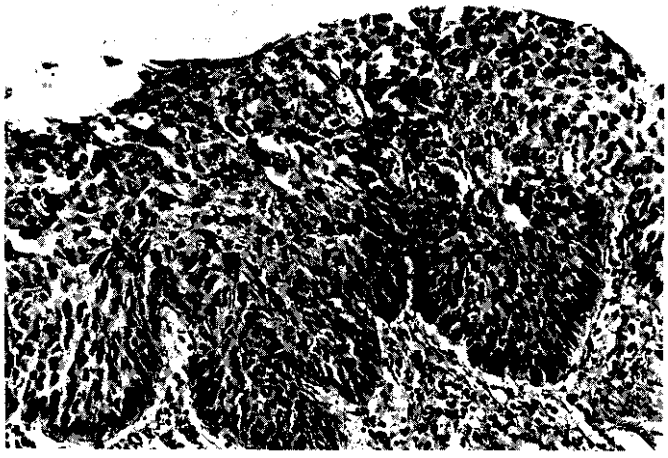
EXAMPLES OF NORMAL AND ABNORMAL BRONCHIAL EPITHELIUM



1. *Normal*



2. Basal-cell hyperplasia--replacement of ciliary epithelium with a thick layer of cells resembling stratified squamous epithelium.



3. Extensive basal-cell hyperplasia with numerous atypical cells.

Source: Auerbach, Oscar. Special communication to the Surgeon General's Advisory Committee on Smoking and Health.

cigarettes smoked. Among non-smokers, lesions composed entirely of atypical cells with loss of cilia were uniformly absent, although a few could be seen with more than two rows of basal cells containing some atypical cells. In contrast, atypical cells were found in all lesions seen in the tracheobronchial tree of patients who smoked two or more packs of cigarettes a day, irrespective of the presence of hyperplasia and/or cilia loss or whether the patients died of lung cancer. The most severe lesion, aside from invasive carcinoma, consisted of loss of cilia, and hyperplasia up to five or more cell rows composed entirely of atypical cells. This lesion was never found among men who did not smoke regularly and was found only rarely among light smokers. However, it was found in 4.3 percent of sections from men

who smoked one to two packs a day, in 11.4 percent of sections from those who smoked two or more packs a day, and in 14.3 percent of sections from smokers who died of lung cancer (15).

While epithelial changes were found in all portions of the tracheobronchial tree, quantitative differences were found between the changes in the trachea and those in the bronchi; hyperplastic lesions consisting entirely of atypical cells without cilia were found in all regions of the bronchial mucosa but only rarely in the trachea. It is notable that cancer rarely occurs in the trachea.

In 35 children less than 15 years of age, Auerbach et al. (16) found the same percent of epithelial changes in the tracheobronchial tree as in the same numher of adults who had never smoked regularly (16.6 percent of children and 16.8 percent of adults). No hyperplasia with atypical cells was seen in any section.

Later, Auerbach et al. (15a.) studied the morphology of the tracheobronchial tree from 302 women and 456 men with respect to additional variables—sex, age, pneumonia, and amount smoked. One or more epithelial lesions were found in 68.2 percent of sections from men smokers and 68.6 percent from women smokers when matched groups were examined. However, on further study, hyperplastic lesions composed entirely of atypical cells were found in 6.9 percent of the sections from the male group and in 2.5 percent of those from females.

Matched groups of male cigarette smokers of two age groups (averages of 37 and 67 years) were compared. Many more lesions, characterized by a large number of cells with atypical nuclei, were observed in the older than in the younger group. In a parallel study of women who did not smoke (average ages of 46 and 76 years), no difference in the number or type of lesions was noted. Few changes in the bronchial epithelium were found in sections from 27 women non-smokers over 85 years of age.

Occasional atypical changes were found in women non-smokers (a) who died of pneumonia, (b) who died of various other causes but had pneumonia at the time of death, and (c) who died with no evidence of pneumonia. However, basal cell hyperplasia, loss of cilia, and ulceration were found more frequently in sections from women who died with pneumonia than from women who had no evidence of pneumonia. These observations are in agreement with those of other investigators who found metaplasia of the bronchial epithelium to be more frequent in patients with various non-neoplastic pulmonary diseases than in controls without such disease (256, 305, 352, 366).

Far fewer epithelial lesions were found in non-smokers than in pipe, cigar, or cigarette smokers (15a.), the difference being particularly evident in the occurrence of atypical cells. However, sections from pipe and cigar smokers showed fewer epithelial lesions than did sections from cigarette smokers. Cells with atypical nuclei were found far mare frequently in cigarette smokers than in cigar or pipe smokers (Table 7).

In 72 male ex-cigarette smokers who had smoked for at least ten years and had not smoked for at least five years prior to the time of death, there were less hyperplasia, less loss of cilia, and fewer atypical cells than in sections from current cigarette smokers (14). An interesting by-product of this study was the finding of “cells with disintegrating nuclei" in the

TABLE 7.—*Changes in bronchial epithelium in matched triads of male non-smokers and smokers of different types of tobacco.*[1]

Group	Number of subjects	Total sections with epithelium	Sections with 1 or more epithelial lesions		3+cell rows with cilia present		Cilia absent		Atypical cells present		Atypical cells present with cilia absent		Entirely atypical cells with cilia absent [2]	
			Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
7th set (none vs. pipe vs. cigarette)[3]														
Non-smokers	20	985	214	21.7	110	11.2	101	10.3	26	2.6	3	0.3	0	----------
Pipe smokers	20	924	605	65.5	352	38.1	117	12.7	342	37.0	29	3.1	0	----------
Cigarette smokers	20	914	885	96.8	810	88.6	116	12.7	870	95.2	111	12.1	35	3.8
8th set (none vs. pipe vs. cigarette)														
Non-smokers	25	1,246	285	22.9	167	13.4	132	10.6	9	0.7	1	0.1	0	----------
Pipe smokers	25	1,164	800	68.7	451	38.7	172	14.8	445	38.2	38	3.3	0	----------
Cigarette smokers	25	1,126	1,084	96.3	999	88.7	238	21.1	1,008	89.5	205	18.2	70	6.2
9th set (none vs. cigar vs. cigarette)														
Non-smokers	35	1,706	467	27.4	216	12.7	281	16.5	14	0.8	3	0.2	0	----------
Pipe smokers	35	1,733	1,573	90.8	694	40.0	247	14.3	1,275	73.6	173	10.0	5	0.3
Cigarette smokers	35	1,526	1,511	99.0	1,414	92.7	428	28.0	1,493	97.8	417	27.3	196	12.8

[1] Modified table from Auerbach et al. (15a).
[2] Carcinoma in situ
[3] Triads were matched for age, occupation, residency and (for smokers) by amount of tobacco used.

bronchial epithelium of 43 out of 72 ex-smokers. These cells were not found in the bronchial epithelium of current cigarette smokers or non-smokers. They were considered by Auerbach et al. to be pathognomonic of the ex-smoker.

Many of the histopathologic findings observed by Auerbach et al. in the bronchial epithelium of smokers have been confirmed by other investigators (64, 155, 189, 304).

The significance of the hyperplastic changes in the bronchial epithelium for the pathogenesis of lung cancer in smokers is not fully understood. The establishment of a link between the hyperplastic changes and the subsequent development of lung cancer would relate smoking causally to lung cancer. However, the non-specificity of hyperplasia of the bronchial epithelium is universally recognized. Furthermore, similar changes are known to be reversible.

On the other hand, evidence from both human and experimental observations points strongly to the conclusion that some hyperplastic changes of the bronchial epithelium, especially those with many atypical alterations, are probably premalignant.

It is well documented that the bronchial trees of patients with lung cancer have areas, sometimes very widespread, of epithelial hyperplasia containing many atypical and bizarre cells. This was reported by Lindberg in 1935 (216) and by many other investigators (10, 12, 28, 52, 134, 265, 285, 349, 370). Black and Ackerman (28) have carried out an extensive study of the relationship between metaplasia and anaplasia and lung cancer in human lungs and have presented strong circumstantial evidence for the opinion that the basal cell hyperplasia with advanced atypical changes and loss of cilia (the so-called carcinoma in-situ) represent a stage in the development of lung cancer. They also emphasized, as has Auerbach et al. (12), the frequent occurrence of atypical basal cell hyperplasia at multiple sites in the bronchial tree considerably removed from the site of the lung cancer. They have pointed out the similarities between the atypical hyperplasias in the tracheobronchial tree and carcinoma in-situ in other sites, such as the cervix, skin, and larynx.

Lung cancer was induced in animals by radioactive substances (198, 217), chemical carcinogens (198, 340), and air pollutants plus influenza virus (191). These studies have demonstrated the occurrence of extensive atypical hyperplastic changes in the bronchial epithelium of experimental animals preceding the appearance of lung cancer. The changes described are, on the whole, similar to those seen by Auerbach et al. in the bronchial epithelium of heavy cigarette smokers and by others in patients with lung cancer. The hyperplastic lesions in animals do not invariably develop into cancer. This appears to be the case also in man (14).

In view of these observations, it seems probable that some of the lesions found in the tracheobronchial tree in cigarette smokers are capable of developing into lung cancer. Thus, these lesions may be a link in the pathogenesis of lung cancer in smokers.

SUMMARY.--Several types of epithelial changes are much more common in the trachea and bronchi of cigarette smokers, with or without lung cancer, than of non-smokers and of patients without lung cancer. These epithelial

changes are (a) loss of cilia, (b) basal cell hyperplasia, and (c) appearance of atypical cells with irregular hyperchromatic nuclei. The degree of each of the epithelial changes in general increases with the number of cigarettes smoked. Extensive atypical changes have been seen most frequently in men who smoked two or more packs of cigarettes a day. Hyperplasia without atypical changes was seen in the bronchial tree of children under 15 years of age and in women non-smokers at all ages who died with pneumonia. Women cigarette smokers, in general, have the same epithelial changes as do men smokers. However, at given levels of cigarette use, women appear to show fewer atypical cells than do men. Older men smokers have many more atypical cells than do younger men smokers. Men who smoke pipes or cigars have more epithelial changes than do non-smokers, but have fewer changes than do cigarette smokers consuming approximately the same amount of tobacco. Male ex-cigarette smokers have less hyperplasia and fewer atypical cells than do current cigarette smokers.

CONCLUSION.—It may be concluded on the basis of human and experimental evidence that some of the advanced epithelial hyperplastic lesions with many atypical cells, seen in the bronchi of some cigarette smokers, are probably premalignant.

TYPING OF LUNG TUMORS

Historical aspects of the typing of lung tumors in relation to possible etiolopical agents are reviewed in the section on Retrospective Studies, Histologic Types.

Kreyberg (195, 196) noted that the increase of lung cancer in recent decades seemed to occur for only certain types of lung cancers (his Group I). and that other types did not increase (his Group II). Kreyberg's classification is compared with the World Health Organization classification in Table 8. His Group I includes epidermoid carcinomas and small-cell anaplastic carcinomas. His Group II includes adenocarcinomas and a few rare types. He postulated that a determination of the ratio between Groups I and II is a good index of the occurrence and magnitude of an increase in lung cancer in a given locality and his epidemiologic studies linked the increase almost entirely to the use of cigarettes. His thesis has been accepted by many while disputed by others.

The results of the study of lung cancer at Los Angeles County General Hospital (LACGH) by Herman and Crittenden (167) did not confirm Kreyberg's conclusions. These investigators, analyzing the autopsy data on lung cancer from 1927 to 1957 at LACGH, observed a marked increase in the number of lung cancer cases as had been noted by many other investigators. However, the ratio of Kreyberg's Group I to Group II had not changed perceptibly over this period and was notably lower than in other series studied.

The Committee on Smoking and Health sponsored a workshop in which slides from coded cases of lung cancer from four different institutions in three areas of the United States were typed "blind" by Dr. Kreyberg and pathologists from the cooperating institutions.[1] There was good agreement as to typing. The low ratio of Group I to Group II cancers at LACGH was confirmed. When typing of the reviewed cases was compared with smoking

[1] Workshop on typing of lung tumors held in Washington, D.C., April 11, 1963.

TABLE 8.—*Relation between WHO and Kreyberg classifications of lung tumors*

WHO classification [1]	Kreyberg classification [2]
A *Epithelial Tumors*	
1. Epidermoid carcinomas	Group I
a highly differentiated	
b. moderately differentiated	
c slightly differentiated	
2. Small-cell anaplastic carcinomas	Group I
a. with oval-cell structure ("oat-cell" carcinoma)	
3. Adenocarcinomas	Group II
a. acinar (with or without formation of mucus)	
b papillary (with or without formation of mucus)	
c. tumors with a predominance of "large cells" some of which show formation of glands and/or production of mucus	
4. Large-cell undifferentiated carcinomas	Other [3]
5. Combined epidermoid and adenocarcinomas	Other
6. Bronchiolo-alveolar cell carcinomas	Group II
7. Carcinoid tumors (solid, trabecular, alveolar)	Group II
8. Tumors of mucous glands	Group II
a cylindroma	
b muco-epidermoid tumors	
9 Papillomas of the surface epithelium	Other
a epidermoid	
b. epidermoid with goblet cells	
B. *Sarcomas*	Other
C. *Combined Tumors of Epithelial and Mesenchymal Cells*	Other
D. *Mesotheliomas of the Pleura*	Other
1. Localized	
2. Diffuse	
E. *Tumors Unclassified*	

[1] Committee on Cancer of the Lung, World Health Organization.
[2] Kreyberg, L. Histological Lung Cancer Types A Morphological and Biological Correlation. Norwegian Universities Press, 1962.
[3] Types marked "other" are not included in either of Kreyberg groups.

histories, moreover, it became evident that both Group I and Group II were increased among heavy smokers.

Several factors were recognized to influence Group I/Group II ratios: (a) source of material (for example, significant differences in the ratio were found between autopsy and surgical materials, and between surgical materials obtained by biopsy and by resection during operation for lung cancer); (b) failure to autopsy certain cases which were judged to be inoperable (the patient being sent home as incurable) ; (c) the fact that Group I (squamous and oval-cell) carcinomas are more likely to be among the operable cases and among those accessible to bronchoscopy, and (d) variations in selection of patients in different institutions.

An independent review of the histopathology of 1,146 lung cancer cases from the U.S. veterans study (policyholders) by Dorn, Herrold and Haenszel (Table 9) (89) showed high mortality ratios for both Group I and Group II cancers in current heavy smokers (over 20 cigarettes/day), although Group I had a higher mortality ratio (31.2) than Group II (7.2).

Another study of Haenszel on white females (152), as well as studies of female patients at Massachusetts General Hospital (54), Roswell Park Memorial Institute (133), Presbyterian Hospital (323), and Washington University (260), indicated that adenocarcinoma is also contributing to the increment of lung cancer in women.

CONCLUSIONS—(a) The histological typing of lung cancer is reliable. However, the use of the ratio of Group I and Group II is an index to the magnitude of increase in lung cancer is of limited value.

TABLE 9.-- *Mortality ratios for cancer of the lung by smoking class and by type of tumor, U.S. veterans study*

	All Deaths	Group I	Group II
Nonsmokers [1]	1.0	1.0	1.0
Pipe and/or cigar smokers	1.5	2.2	0.6
Cigarette smokers, total [2]	8.2	15.4	5.1
Current			
Total	10.0	18.9	5.8
≤20 cigarettes/day	7.1	12.9	5.1
>20 cigarettes/day	16.0	31.2	7.2
Discontinued (By Maximum Amt. Ever Smoked)			
Total	4.7	8.4	3.7
≤20 cigarettes/day	3.5	6.6	2.7
>20 cigarettes/day	7.4	12.1	5.6

[1] Includes occasional smokers.
[2] Includes men who were using pipe and/or cigars in addition to cigarettes.

Source: Dorn, H. F., Haenszel, W. and Herrold, K. (89) (see Chapter 8 also).

(b) Squamous and oval-cell carcinomas (Group I) comprise the predominant types associated with the increase of lung cancer in both males and females. In several studies, adenocarcinomas (Group II) have also increased in both sexes although to a lesser degree.

Evaluation of the Association between Smoking and Lung Cancer

It is not practical to attempt an experiment in man to test whether a causal relationship exists between smoking of tobacco and lung cancer. Such an experiment would imply the random selection of very young subjects living under environmental conditions as nearly identical as possible, and random selection of those who were to be smokers and those who were to be the non-smoker controls. Their smoking and other habits would need to be held constant for many years. Because of the relatively low incidence of lung cancer in the human population, both the test and the control groups would have to be very large.

As such an experiment in man is not feasible, the judgment of causality must be made on other grounds. The epidemiologic method, when coupled with clinical or laboratory observations, can provide the basis from which judgments of causality may be derived.

INDIRECT MEASURE OF THE ASSOCIATION

The crudest indicators of an association between lung cancer and smoking are certain indirect measures: (a) a correlative increase in lung cancer mortality rates and in per capita tobacco consumption in a number of countries (76, 138, 211, 239, 255), and (b) disparities between male and female lung cancer mortality rates correlated with corresponding differences in smoking habits of men and women, both by amounts smoked and duration of smoking (65, 151, 344).

Figure 9 shows a correlation of crude male death rates from lung cancer in 11 countries in 1950 with the per capita consumption of cigarettes in these countries in 1930 as presented by Doll (76). Assuming a 20-year induction period for the appearance of lung cancer, Doll found a significant correlation (0.73±0.30) between the death rates and cigarette consumption. Since virtually all the tobacco consumption in 1930 was among men in the countries

CRUDE MALE DEATH RATE FOR LUNG CANCER IN 1950 AND PER CAPITA CONSUMPTION OF CIGARETTES IN 1930 IN VARIOUS COUNTRIES.

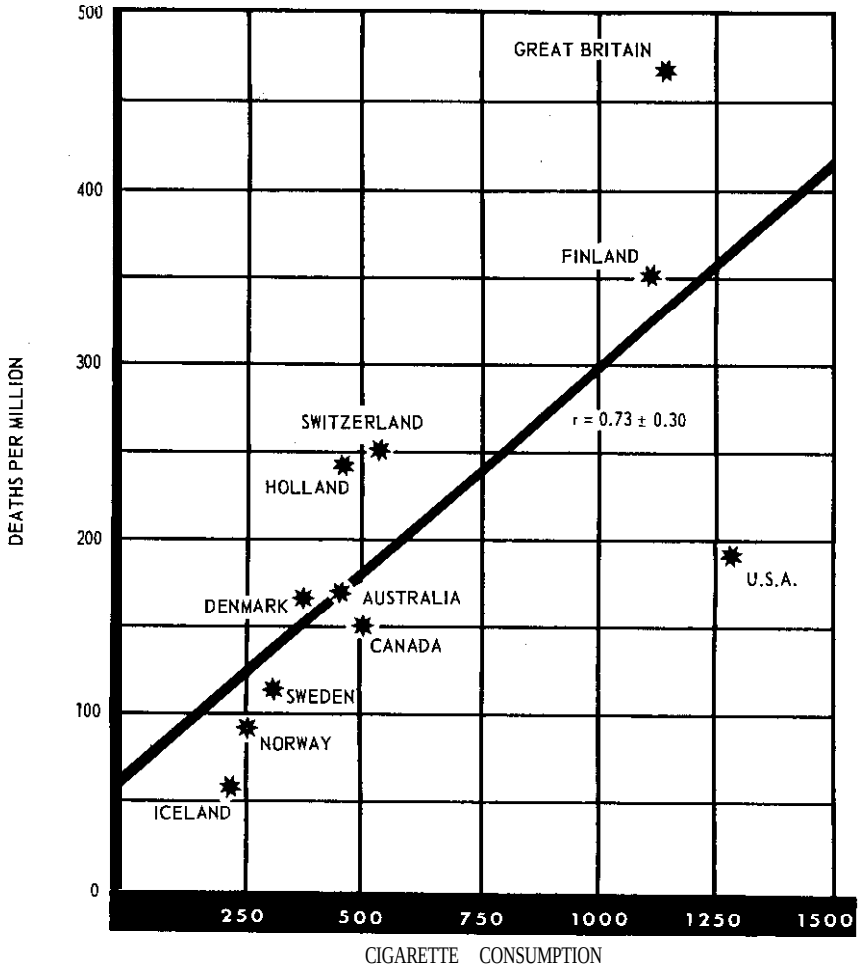


FIGURE 9.

Source: Doll, R (76)

represented (Great Britain, Finland, Switzerland, Holland, the United States, Australia, Denmark, Canada, Sweden, Norway, and Iceland), it seemed reasonable to compare the annual per capita consumption of each country with the crude, male lung cancer death rates.

It will be noted in Figure 9 that the data from the United States show a relatively low death rate in relation to cigarette consumption. Doll suggested two explanations: the influence of a higher proportion of young

people in the U.S. population and the method of smoking, with the U.S. smokers consuming less of each cigarette than the British smokers. Since Doll's explanations of the discrepancy, additional information has become available. Studies on length of cigarette butts discarded have shown American discards to be significantly longer than British discards; 30.9 mm (156) and 18.7 mm (85) respectively. Also, there is a significantly greater percentage of smokers in Great Britain than in the United States in the age groups in which lung cancer occurs at high rates (52.6 percent in 60+ year age group and 29.2 percent in 65+ year age group respectively).

Strictly comparable data do not exist on inhalation practices for the two countries. Such information would aid in explaining this discrepancy as well as a similar disparity between Holland and Great Britain. In Holland (156) the length of the cigarette butts was almost the same as in Great Britain (19.7 mm), but the crude male lung cancer death rate in Holland was significantly lower than in Great Britain. This correlates well, as shown in Figure 9, with the annual per capita consumption of cigarettes in Holland which has been much lower than in Great Britain.

It should be mentioned that differences in intensity of air pollution and industrial exposures in these countries have not been taken into account. However, for reasons given below, these latter factors do not account for the magnitude of the difference in incidence of lung cancer nearly as well as the amount of each cigarette smoked and the degree of inhalation. Finally, the varying composition of the tobacco in the several countries was not considered in these studies.

An elaboration of the disparities between male and female lung cancer mortality rates and their correlation with differences in smoking patterns is also in order, for the sex disparity has also been posed as contradictory to the smoking-lung cancer hypothesis. Although the opponents of the hypothesis, pointing to the sex disparity (116, 229), have minimized the differences in smoking habits, the fact remains that the magnitudes of the differences are quite large. In a representative cross-sectional survey of smoking habits coupled with the Current Population Survey of the Bureau of the Census in 1955, Haenszel, et al. (151) found the following disparities between male and female smoking patterns:

1. Whereas only 22.9 percent of males had never smoked, 67.5 percent of females had not.
2. Males showed relatively little variation among the component age groups in percentage not smoking, whereas females after age 25-34 showed a consistently increasing percentage of non-smokers in successively higher age groups (Figure 10).
3. Sixty-five percent of males smoked cigarettes as compared with 32 percent of females.
4. Cohort analyses revealed the adoption of cigarette smoking late in life for both males and females among cohorts born before 1890; but male cohorts born after 1900 successively began to smoke earlier in life. Large-scale adoption of cigarette smoking by women did not occur until the decades of the 1920's and 1930's.

PERCENTAGE OF PERSONS WHO HAVE NEVER SMOKED, BY SEX AND AGE, UNITED STATES, 1955

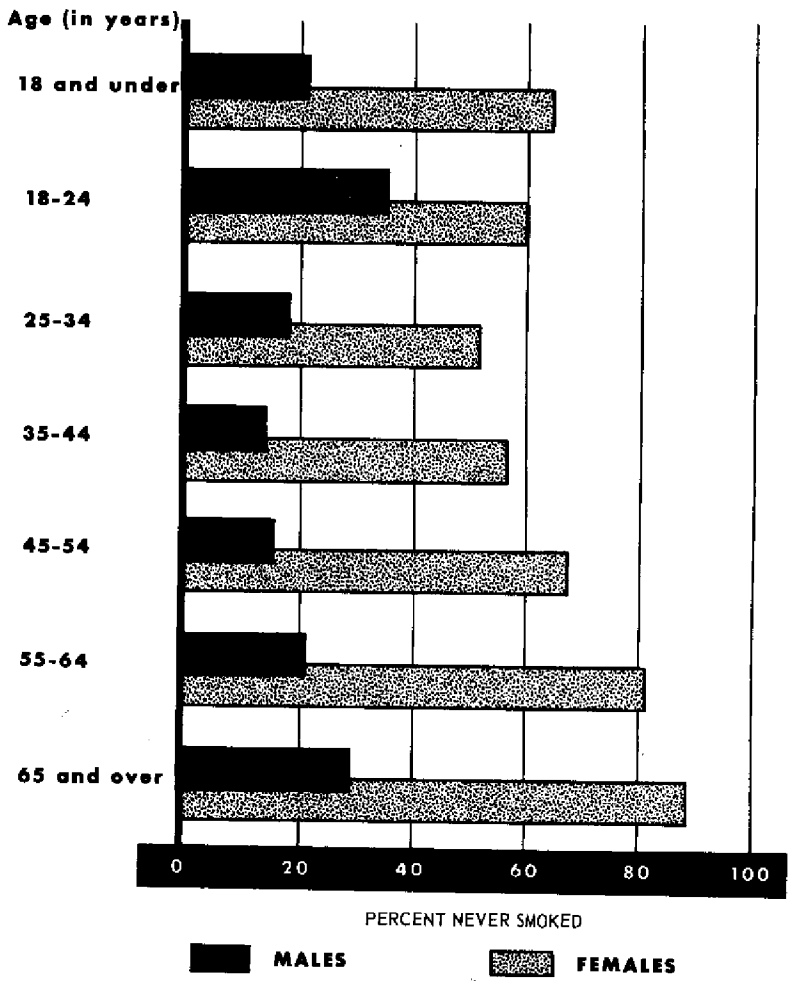


FIGURE 10.

Source: Haenszel, W. M. et al. (151)

5. The median age at which males started smoking has remained fairly stable for the several age cohorts: from 19.3 years for ages 65 and over to 17.9 years for age 25-34; the median age that females started smoking has dropped dramatically from 39.9 years for the age group 65 and over to 20.0 years for age 25-34.
6. Males in all age groups smoked considerably more cigarettes per day than did females. In ages 55 and over, 6.9 percent of the

males smoked more than a pack a day, compared with only 0.6 percent of the females. Although urban-rural and geographic regional differences were noted, significant disparities between male and female smoking were maintained throughout. Thus it can readily be deduced that these findings are consistent not only with the sex disparity in lung cancer mortality but also with the slower but nevertheless continuing rise in female lung cancer mortality.

British studies (344) also revealed that females, especially before World War II, consumed much less tobacco than did males. A correction for the marked disparity in smoking habits of males and females reduced the observed 5-fold excess of male lung cancer deaths to a 1.4-fold excess as of 1953 (149). Supporting this finding are the data from two retrospective studies (147, 152) in which the age-adjusted lung cancer death rates in 1958-59 among male and female non-smokers were 12.5 and 9.4, respectively for a ratio of 1.33 (145). This residual ratio implies that there may be other factors operating to produce a portion of the sex differential in mortality.

DIRECT MEASURE OF THE ASSOCIATION

For a direct measure of the association between lung cancer and smoking it is, of course, essential that both variables or attributes be measured in the same populations. The 29 retrospective studies, described earlier, consider smoking (usually kind, amount, and duration) and non-smoking among cases of lung cancer and individuals without lung cancer. The seven prospective studies consider the occurrence or lack of occurrence of lung cancer among smokers and non-smokers.

ESTABLISHMENT OF ASSOCIATION.--A number of investigators, though accepting the existence of an association, have questioned its significance in terms of a causal hypothesis (58, 102, 114, 115, 116, 117, 141, 178, 218, 219, 287, 288, 298, 299). Some of these doubts have been on the basis of a possible genetic underlay which might determine both smoking and lung cancer (114, 115, 116, 117). Some have followed contradictory observations in the dissenter's own work (58, 102, 141), incorrectly assessed evidence of lung cancer mortality trends, or the belief that the causal hypothesis requires cigarette smoking to be the sole cause of lung cancer (178, 287, 288). Others believe that the lung cancer rise is spurious and can be attributed either to improvements in diagnosis and reporting (218, 219, 287, 288, 298, 299) or to the aging of the population. In the latter explanation they ignore the fact that aging of the population does not affect age-specific mortality rates which, for lung cancer, are also rising with the passage of time. Still others express doubt on the basis of the lack of a concomitant rise in cancers of the oral cavity (178, 298) or of the skin of the fingers (178). Finally, some doubts have been based on supposed incongruencies between the cigarette-smoking hypothesis and urban-rural as well as sex differences in lung cancer mortality (116, 178, 229). There are a few investigators who maintain that the association may be spurious or that it has not been proved (22, 23, 24, 228, 229, 230).

A number of these objections have been assessed in earlier discussions in this section; others will be evaluated below. These latter criticisms have revolved about defects inherent in the retrospective or the prospective

methods of approach, biases of selection in either method, biases of non-response, the validity of the results in the early phases of a prospective study, and the misclassification of both variables: smoking habits and lung cancer.

It should be noted that the Current Population Survey of 1955 yielded results highly consistent with data on tobacco production and taxation (151) ; that classification errors in terms of amount of smoking were relatively minor in a reliability study by Finkner (113) ; and that, in at least three prospective studies, in which subjects were requestioned on smoking habits at intervals of at least two years, the replies were closely reproducible (87, 88, 157, 159, 162, 163), particularly if no illness had intervened (159).

With regard to the retrospective studies, it has also been suggested that knowledge of the illness might have introduced bias in relation to histories of smoking habits (158, 229). In at least one retrospective study, both patient and interviewer were unaware of the diagnosis of lung cancer, the smoking histories having been obtained before the diagnosis was made (207). Furthermore, patients initially believed to have lung cancer who, after interview, were found not to have the disease, reported smoking histories similar to the control groups and not the lung cancer groups (84). Finally, this bias cannot have influenced the findings of several studies in which a significantly greater proportion of cigarette smokers and heavy cigarette smokers were associated with epidermoid cancers than with adenocarcinoma (86, 150, 163, 313, 375). The reliability of response to smoking history would thus appear to be markedly above the critical level for the firm establishment of an association by the retrospective method. In prospective studies, this factor is less of a problem.

In retrospective studies the investigator can confine himself to cases with accurate diagnoses. In the prospective approach, accuracy of diagnosis may not always be attainable, but all cases must be included. In assessing the results of the prospective studies it must be kept in mind that all deaths from any cause were involved in the calculations, with the cigarette smoker rates higher than those for non-smokers and with a gradient by amount of smoking demonstrated in all of the studies. Evidence that the specific estimates of risk for lung cancer among smokers actually might have been underestimated has been presented by Hammond and Horn (162, 163), who found higher relative risk ratios among smokers for confirmed cases than for those with Iess well-established diagnoses. Most of the prospective studies yield relative risks of lung cancer by various smoking categories which approximate those found in the Doll and Hill physician study (83) where, obviously, diagnostic evidence would be more readily available than in the general population. It would thus appear that in the data from retrospective and prospective studies,diagnostic accuracy was not a critical factor in the establishment of an association between smoking and lung cancer.

The question of *selection bias* is, of course, a more complicated problem. Several criticisms have been leveled at both the retrospective and prospective methods. Although in retrospective studies the selection of a control group may pose a more serious problem, even the selection of the case material may interject difficulties. It has been claimed by Berkson (24) that the selection of hospitalized cases may lead to bias if smokers with lung cancer

were more often hospitalized than non-smokers with the disease. However, nearly all lung cancer cases are hospitalized, a point which, he concedes, would thus minimize this bias. Furthermore, several retrospective studies have surveyed all the cases in the area regardless of hospitalization (238, 335), or all deaths regardless of cause or hospitalization (379).

Another criticism of patient selection in retrospective studies deals with the danger that, in studies highly cross-sectional in time, if smokers live longer than non-smokers. there would obviously be more smokers in the disease group, and thus a spurious association of disease with smoking would result (254). There is no evidence for this basic assumption. Furthermore, it is inapplicable because almost all the retrospective studies were actually based on newly diagnosed cases collected serially over an interval of time long enough to remove this bias.

Control groups pose a problem in retrospective studies. In 27 of the 29 retrospective studies (exceptions are references 147 and 152) the controls were subjects without lung cancer, such as patients with other cancers, with diseases other than cancer, or so-called normals selected from the population. Analysis of the prospective studies proved that the biases interjected by the selection of sick controls in the retrospective studies actually operated to produce an underestimation of the association, for it has been shown that a number of other diseases are also associated with smoking. Furthermore, several studies have, in addition to controls with other diseases, selected a second set of random controls from the genera1 population (82, 150, 222), only to find that the association utilizing sick controls, significant though it proved to be, was intermediate to the association utilizing random population controls.

The problem of selection bias in prospective studies is much more subtle, since there may be self-selection on the basis of illness existing at the time the study begins. This is essentially a problem of non-response which has been handled in detail in Chapter 8. The character of this non-response presents at least two nuances: a combination of self-selection and operator selection, as in the volunteer studies of Hammond and Horn (162) and Hammond (157) and the response to questionnaires in a total population study such as Dorn's (88).

Suffice it to say at this point that, regardless of whether there is over-representation of sick smokers or well non-smokers or both in a prospective study, with the passage of time more deaths of sick persons would occur (without regard to the independent variable of smoking). Thus the death rates of smokers would tend to approach the death rate of non-smokers, removing the original selection bias and providing greater confidence in the residual association of the death rate with smoking if it persisted. In two of the studies (157, 162, 163) exclusion of ill persons on entry did take place. Further, in the studies that provide this comparison, the high lung cancer mortality ratio of cigarette smokers was maintained with the passage of time. In the Dorn study the mortality ratio was 9.9 after three years experience and 12.0 after six years experience; the Hammond study gave 9.0 after 10.5 months (157) and 9.6 after 22 months, while Doll and Hill (84) showed that the gradient of increase in lung cancer death rate with increasing amount smoked appeared consistently in each of the first four years of their study,

This also weakens the criticism by Mainland and Herrera (230) of the use of non-professional volunteer workers for subject selection.

Thus it would appear that an association between cigarette smoking and lung cancer does indeed exist.

CAUSAL SIGNIFICANCE OF THE ASSOCIATION.—As already stated, statistical methods cannot establish proof of a causal relationship in an association. 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 cigarette smoking and lung cancer a number of criteria must be utilized, no one of which by itself is pathognomonic or a *sine qua non* 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 relationship of the association
(e) The coherence of the association.

THE CONSISTENCY OF THE ASSOCIATION.—This criterion implies that diverse methods of approach in the study of an association will provide similar conclusions. It is noteworthy that all 29 retrospective studies found an association between cigarette smoking and lung cancer. The very nature of the criticisms leveled against these retrospective studies indicates a diversity of characteristics of approach and, for that matter, marked differences in shortcomings which have been discussed in detail above. It is indeed remarkable that no reasonably well designed restrospective study has found results to the contrary. Seven prospective studies have also revealed highly significant associations. Where relative risks could be calculated on the basis of some reasonable assumptions in some of the retrospective studies, a consistency not only among them (38, 82, 147, 152, 222, 283, 301, 313, 381) but also with the prospective studies could be demonstrated. Such a situation would prevail if the association were either causal, or spurious on the basis of an unknown source of bias. It is difficult to conceive of a universally acting bias in all the diverse approaches unless it be a constitutional genetic characteristic or one acquired early in life, which will be discussed later in the section, Constitutional Hypothesis.

Two studies of tobacco workers (58, 141) have been cited as inconsistent with the 29 retrospective and particularly the 7 prospective studies cited in detail in the early portions of this section. Both these studies can be dismissed because of major defects in methodology and concept. The heavier smoking among the tobacco workers in these studies was considered, but no comparison of observed-to-expected rates was made on the basis of smoking classes within this population. Furthermore their conclusions are based on expectancies in the general population without regard to the fact that persons with acute, chronic, or disabling illness are initially excluded from employment and that those developing permanent illness are lost to employee rolls.

THE STRENGTH OF THE ASSOCIATION.—The most direct measure of the strength of the association between smoking and lung cancer is the ratio of lung cancer rates for smokers to the rates for non-smokers, provided these two rates have been adjusted for the age characteristics of each group. Another way of expressing this is the ratio of the number of observed cases

in the smoker group to the expected number calculated by applying the non-smoker rate to the population of smokers. This provides us with a measure of relative risk which can yield a judgment on the size *of the effect* of a factor on a disease and which, even in the presence of another agent without causal effect, but correlated with the causal agent, will not be obscured by the presence of the non-causal agent. Cornfield et al. (62) have not only provided us with a detailed analysis of the applications of both absolute and relative measures of risk, but have also demonstrated the useful. ness of the relative risk measure in judging causal and non-causal effects with mathematical proof of their statements.

An absolute measure of difference in prevalence of a disease between populations with or without the agent (e.g., cigarette smoke), where the agent may be causal in its effect on several diseases, can provide us with the means of appraising the public health significance of the disease, i.e. the size of the problem, in relation to other diseases. It is less effective for appraising the non-causal nature of agents having apparent effects, the importance of one agent with respect to other agents, or the effects of refinement of disease classification. This, Cornfield and his co-authors (62) have demonstrated.

In essence, then, a relative risk ratio measuring the strength of an association provides for an evaluation of whether this factor is important in the production of a disease. In the data of the nine retrospective studies for which relative risks of lung cancer among smokers and non-smokers were calculated, the ratios were not only high in all of the studies but showed a remarkable similarity in magnitude. More important, in the seven prospective studies which inherently can reveal direct estimates of risks among smokers and non-smokers, the relative risk ratios for lung cancer were uniformly high and, again, remarkably close in magnitude. Furthermore, the retrospective and prospective studies yielded quite similar ratios.

Important to the strength as well as to the coherence of the association is the dose-effect phenomenon. In every prospective study that provided this information, the dose-effect was apparent, with the relative risk ratio increasing as the amount of tobacco (84) or of cigarettes (25, 88, 96, 97, 163) smoked per day increased (Table 5). Even the retrospective studies for which relative risks were calculated by amount smoked (38, 147, 152, 222) showed similar increases in risks with amount smoked (Table 4).

It may be estimated from the data in the prospective studies that, in comparison with non-smokers, average smokers of cigarettes have a 9- to l0-fold risk of developing lung cancer, and heavy smokers, at least a 20-fold risk. Thus it would appear that the strength of the association between cigarette smoking and lung cancer must be judged to be high.

THE SPECIFICITY OF THE ASSOCIATION.— This concept cannot be entirely dissociated from the concept inherent in the strength of the association. It implies the precision with which one component of an associated pair can be utilized to predict the occurrence of the other, i.e., how frequently the presence of one variable (e.g., lung cancer) will predict, in the same individual, the presence of another (e.g., cigarette smoking).

In a discussion of the specificity of the relationship between any factor possibly causal in character and a disease it may produce, it must be rec-

ognized that rarely, if ever, in our biologic universe, does the presence of an agent invariably predict the occurrence of a disease. Second, but not less important, is our growing recognition that a given disease may have multiple causes. The ideal state in which smoking or smoking of cigarettes and every case of lung cancer was correlated one-to-one would pose much less difficulty in a judgment of causality, but the existence of lung cancer in non-smokers does indeed complicate matters somewhat. It is evident that the greater the number of causal agents producing a given disease the less strong and the less specific will be the association between any one of them and the total load of the disease. But this could not be posed as a contradiction to a causal hypothesis for any one of them even though the predictive value of any one of them might be small. For example, the pathologist who examines a lung at autopsy and finds tubercle formation and caseation necrosis would almost invariably be able to predict the coexistence of tubercle bacilli. Experience has shown that the lesions are highly specific for *Mycobacterium tuberculosis*. On the other hand, a clinician may encounter a combination of signs and symptoms including stiff neck, stiff back, fever, nausea, vomiting, and lymphocytes in the spinal fluid. Experience has revealed that any one of a number of organisms may be associated with this syndrome: polio virus, ECHO viruses, Coxsackie viruses and *Leptospirae*, to name but a few. The predictability of the coexistence of polio virus per se is rather low. In other words, the syndrome as noted is not very specific for polio virus. This may well be the condition which prevails in coronary heart disease where the mortality ratio is between 1.6 and 1.8 or a 60 to 80 percent excess among smokers of cigarettes. If this ratio is applicable to the entire population from which the sample data are derived, another way of expressing this relationship is that, of the total load of coronary heart disease mortality among males only 61 to 64 percent is associated with cigarette smoking. The large residual among non-cigarette smokers implies either other causes in addition to smoking or, as a somewhat greater possibility, factors actually causally related to coronary heart disease and frequently, but not invariably, associated with smoking.

However, in lung cancer, we are dealing with relative risk ratios averaging 9.0 to 10.0 for cigarette smokers compared to non-smokers. This is an excess of 900 to 1,000 percent among smokers of cigarettes. Similarly, this means that of the total load of lung cancer in males about 90 percent is associated with cigarette smoking. In order to account for risk ratios of this magnitude as due to an association of smoking history with still another causative factor X (hormonal, constitutional, or other), a necessary condition would be that factor X be present at least nine times more frequently among smokers than non-smokers. No such factors with such high relative prevalence among smokers have yet been demonstrated.

Another aspect of specificity requires some insight. Several critics of the causal hypothesis have questioned the significance of the association on the grounds that the existence of an association with such a wide variety of diseases, as elicited in the prospective studies, detracts from specificity for any one of them (22, 7). In a sense, this viewpoint is an exaggeration, for not all the specific disease mortality ratios in excess of 1.0 are large

enough to warrant secure judgments of the strength of the association and of causal significance. A detailed discussion of this latter point has been presented in Chapter 8. The number of diseases in which the ratios remain significantly high, after consideration of the non-response bias, is not so great as to cast serious doubt on the causal hypothesis. Even if we were dealing with a single pure substance in the environment, the production of a number of disease entities does not contradict the hypothesis. It is well known that a single substance may have several modes of action on the several organ systems and that neither inhalation nor ingestion implies action restricted to the respiratory or digestive tracts, respectively. In tobacco we encounter a complex of substances whose additive and synergistic characteristics before and after combustion remain inadequately explored. It would not be surprising to find that the diverse substances in tobacco smoke could produce more than a single disease.

Actually, the finding that an excess risk for smokers does not occur for every one of the causes of death reinforces the specificity of the excess risk for those causes where the excess is significant.

Thus, it is reasonable to conclude that the association between cigarette smoking and lung cancer has a high degree of specificity.

TEMPORAL RELATIONSHIP OF ASSOCIATED VARIABLES.—In chronic diseases, insidious onset and ignorance of precise induction periods automatically present problems on which came first—the suspected agent or the disease. In any evaluation of the significance of an association, exposure to an agent presumed to be causal must precede, temporally, the onset of a disease which it is purported to produce. The early exposure to tobacco smoke and late manifestation of lung cancer among smokers, seem, at least superficially, to fulfill this condition. This does not, however, preclude the possibility that such patients who, many years after the initiation of smoking are diagnosed as having lung cancer, may have had the primitive cellular changes or anlage (as postulated by Cohnheim) before the advent of their smoking. However, no evidence has thus far been brought forth to indicate that the initiation of the carcinomatous process in a smoker who developed lung cancer antedated the onset of smoking.

COHERENCE OF THE ASSOCIATION.—A final criterion for the appraisal of causal significance of an association is its coherence with known facts in the natural history and biology of the disease. In the lung cancer-cigarette smoking relationship the following should be noted:

(1.) Rise in Lung Cancer Mortality.—The increases in per capita consumption of cigarettes (76, 138, 211, 239, 255) and the age-cohort patterns of smoking among males and females (151) are highly compatible with a real increase in lung cancer mortality.

(2.) Sex Differential in Mortality.—The current sex differences in tobacco use (151, 160), the pronuonced differences in age-cohort patterns between males and females, particularly in the older age groups—over 55 (151) and over 50 (160)—and the more recent adoption of cigarette smoking by women (151, 344) are all compatible with the high male-to-female ratio of lung cancer mortality and also with the lower ratios of 30 years ago (130). Haenzel and Shimkin (149) developed a statistical model for determining whether the results of the retrospective and prospective studies

"were compatible with the information on distribution of lung cancer and thus valid for generalization to larger populations." Applying their model of scheduled relative risks to data on cigarette consumption by age and sex derived from the Current Population Survey of 1955, their predicted male/female ratio came quite close to the observed ratio in the general population.

(3.) Urban-Rural Differences in Lung Cancer Mortality.—A number of sources in this country (90, 136, 148, 175, 238, 252) and overseas (82, 199, 335) have firmly established the existence of an urban excess in lung cancer mortality. Because of the possible implication of an air pollution effect, this urban lung cancer mortality excess has been cited as either being incompatible with the smoking-lung cancer hypothesis (178, 229) or minimizing its significance (69, 70, 71, 101, 190). The data of the studies of a number of authors have clearly shown, however, that although adjustment for smoking history does not equalize the urban-rural lung cancer mortality ratio (149), control on the urban-rural residence factor nevertheless leaves a large mortality risk difference between smokers and non-smokers. Haenszel has demonstrated this fact in his two population sample studies on males and females (147, 152). Mills and Porter (238) demonstrated a much greater effect of smoking on lung cancer mortality than the urban-rural factor. Stocks (335) also demonstrated that though smoking is not the sole factor, as manifested by a rural-urban gradient among non-smokers, it represented a much more preponderant factor in accounting for the lung cancer mortality than did presumed air pollution or at least urbanization. He noted that his regression lines on amount smoked were parallel for the different areas in England and North Wales and that the urban-rural mortality ratios declined from 2.3 among non-smokers and 2.5 among light cigarette smokers to unity among heavy smokers. The first prospective study of Hammond and Horn (162) also showed higher lung cancer mortality rates irrespective of residence. In Dean's second study in South Africa (70), in which he corrected the critical defect in his first study of not studying the smoking habits of the test populations, he continued to emphasize urbanization or air pollution as the major factor in lung cancer. A perusal of his data, however, shows that by controlling on smoking, the lung cancer mortality rates are doubled by the factor of country of origin; whereas, with country of origin controlled, the lung cancer risk increases from 3 to 20 times as the amount of cigarette smoking increases. After smoking patterns are controlled, the residuals in the urban over rural excess imply other factors, although the smoking factor preponderates in the urban-rural differences in lung cancer mortality in all of these studies. Thus the urban excess of lung cancer mortality is not incompatible with the smoking-lung cancer hypothesis.

(4.) Socio-Economic Differentials in Lung Cancer Mortality.—Distinct socio-economic differentials have been demonstrated convincingly in the epidemiology of lung cancer. Cohart (57) found a 40-percent excess of lung cancer incidence among the lowest economic class (both sexes) in the New Haven population, and the morbidity survey by Dorn and Cutler (90) demonstrated a distinct gradient by income class among white males, with the highest rates among the lowest income groups. In Denmark, Clemmesen and Nielsen, utilizing data derived from the Danish Cancer Registry, also

found a much higher incidence of lung cancer among males in the lower rental groups (55). In relation to the contribution which smoking makes to this differential, there is evidence that cigarette smoking may be inversely related to socio-economic status. The components of socio-economic status are, at best, difficult to define, compartmentalize. and measure. Direct inquiries of family income are rare and, when made, are subject to considerable error. Studies based on rental values, as in the Danish studies. express more adequately socio-economic status.

Another high correlate of income is educational achievement, which has been considered by Hammond in his current prospective study (161) in relation to smoking habits. Among males, the highest proportion of cigarette smokers (past or present) and the highest proportion of those smoking 20 or more cigarettes per day (past or present) were found in the group classified as "some high school education (but not high school graduates)," whereas the lowest proportion was found among college graduates. The highest proportion of ex-cigarette smokers (as of 1961-62) was among college graduates. Although the relation of smoking and educational level in women is more complicated, the group which had been to college also had the highest proportion of ex-smokers. Finally, college graduates had the next to the lowest proportion of heavy cigarette smokers. None of the female gradients was a sharp as those for the men.

Occupation has also been utilized as a measure of socio-economic status. but this measure obviously has severe limitations. No definitive study has been reported in which lung cancer has been correlated with occupation and smoking class; the current Hammond (157) and Dorn (88) prospective studies may ultimately yield definitive findings in this regard. Huwever, some indirect evidence of a partial correlation between the observed higher lung cancer death rates in lower socio-economic groups may be found in Table 26 of the Survey of Tobacco Smoking Patterns in the United States (151). Keeping in mind that type of occupation is not a critical index of income, it will nevertheless be noted that the professional and farmer and farm manager groups had higher proportions of non-smokers among them than did the laborers and craftsmen. This finding is in the proper direction for compatibility with the socio-economic differential in lung cancer mortality but the disparity does not appear to he sufficient to provide a satisfying correction. In fact, in this U.S. study, analyses by amount of cigarettes smoked tended to obscure the ordering by social class. In Great Britain, however, the inverse relationship of socio-economic class to heavy cigarette smoking remained apparent (174) . In the U.S. study, classification by industry showed the highest proportions of non-smokers to be in the professional and agricultural groups and the lowest among industries. Thus, though the measures are admittedly crude, they are compatible with the socioeconomic differential in lung cancer mortality.

(5.) The Dose-Response Relationship.—If cigarette smoking is an important factor in lung cancer, then the risk should be related to the amount smoked, amount inhaled, duration of smoking, age when started smoking, discontinuance of smoking, time since discontinuance, and amount smoked prior to discontinuance. Herein lies the greatest coherence with the known facts of the disease. In almost every study for which data were adequate

and which was directed to amount of smoking, duration of smoking and age when smoking was begun, the associations or calculated relative risks (direct or indirect) revealed gradients in the direction of supporting a true dose effect. Where discontinuance, time since discontinuance, and amount smoked prior to discontinuance were considered in either retrospective studies or, with more detail, in prospective studies, these all showed lower risks for ex-smokers, still lower risks as the length of time since, discontinuance increased, and lower risks among ex-smokers if they had been light smokers. These findings have been described in detail in the section on Retrospective Studies.

Some contradictory information has been presented in regard to inhalation of tobacco smoke. This is the lack of association between inhalation and lung cancer as noted by Doll and Hill (82) alluded to earlier. These authors have begun collecting data (in their prospective study) on inhalation for the mortality experience since 1958. These data are not presently available (80). However, until the current ongoing prospective studies will have yielded information on this point in regard to lung cancer, four retrospective studies provide information on inhalation contrary to the Doll and Hill early negative findings (38, 211, 222, 313). In two of these (222, 313) inhalation and amount of smoking were considered and led to the provocative, finding that with increase in daily amounts of cigarettes smoked the differences in risks between inhalers and noninhalers diminished. There is no immediate explanation for this apparent discrepancy.

Hammond has studied the smoking habits of the men and women in his current prospective study quite intensively (160). He has observed that the majority of men (92.9 percent) who smoke cigarettes inhale, and of these the majority inhale "moderately" to "deeply." Pipe or cigar smokers inhale rarely. Combination smokers (i.e., cigarettes in combination with pipes and/or cigars) inhale in proportions intermediate to these. These findings become compatible with the hypothesis that the degree of inhalation accounts for a gradient of lung cancer risks, high to low, for smokers of cigarettes only, combination smokers, and pipe or cigar smokers (Table 5). An explanation of the diminishing differences in risks between "inhalers" and "noninhalers" with increase in amount smoked might be obtained if a more objective measure of inhalation were available.

(6.) Localization of Cancer in Relation to Type of Smoking.--Although historically a relationship between cancer and smoking was suspected by Holland (176) and Soemmerring (322) with reference to the lower lip, it was not until the systematic, controlled study of lung, lip, pharynx, esophagus, colon and rectum cancers in relation to types of smoking by Levin in 1950 that significantly distinctive associations between localization of the cancer and type of smoking were elicited (207). Levin noted that statistical significance was achieved for cigarette smoking and lung cancer and for pipe smoking and lip cancer and stated, "It is somewhat surprising that type of smoking is the associated factor, rather than the actual use of tobacco." Since then other studies have pointed up the relationship between type of smoking and localization of cancer. Sadowsky (301) in relative risk estimations of types of smoking and cancer site, also noted the highest significant values for cigarettes with lung, larynx and esophagus; for pipes with lip,

tongue and oral cavity; and for cigars with tongue and oral cavity. The complexities involved in a rational explanation for these phenomena are legion, especially since critics of the smoking-lung cancer hypothesis would point to no phenomenal rise of laryngeal cancer (only a slight rise for whites between 1930 and 1955) in the face of increased cigarette consumption. Although among cigarette smokers, the relative risk of mortality from lung cancer is presently greater than the relative risk for laryngeal cancer, the reverse seems to be true among cigar and pipe smokers (Chapter 8, Tables 19 and 24). Furthermore, the per capita rise in cigarette consumption has been accompanied by a concomitant decline in consumption of pipe and cigar tobacco, the smoke of which was not deeply inhaled. It is thus conceivable that the increase in cigarette consumption (and decline in cigar and pipe smoking) could affect an increase in lung cancer more significantly than in laryngeal cancer.

Finally, there is no reason to assume that the susceptibility of the larynx to cancer equals that of the bronchus. Thus, a reasonable explanation for the difference in localization and relative risk is apparent, especially when it is known that in certain industrial exposures in which the irritant is inhaled and lung cancer is associated with such inhalation (chromates), laryngeal and tracheal cancer is rare. It is, on the other hand, easier to visualize a mode of action for pipe and cigar tobacco in production of lip and tongue and other oral cavity cancers. Thus, none of these considerations detract from the coherence of the association between cigarette smoking and lung cancer.

HISTOPATHOLOGIC EVIDENCE

In earlier sections of this Chapter it has been noted that the application of tobacco extracts, smoke or condensates to the lung or trachebronchial tree of experimental animals has failed to produce bronchogenic carcinoma, except possibly in dogs (289). In addition, no animal experiments have thus far been devised to duplicate precisely the act of smoking as it is practiced by man. However, that the lungs of experimental animals are susceptible to carcinogens, particularly polycyclic aromatic hydrocarbons isolated from tobacco smoke, has been demonstrated by a number of workers (5, 197, 302). Of immediate import to the smoking-lung cancer relationship is the observation that the histopathologic characteristics of the cancers thus produced are similar to those observed in man and are predominantly squamous in type. Furthermore, certain bronchial epithelial changes, sequentially observed prior to the malignant changes in animals exposed to these carcinogens are similar to those in the bronchial epithelium of human smokers (9). In this latter extensive and well-controlled study, these changes were rarely seen among non-smokers, but increased in frequency and intensity with the number of cigarettes smoked daily by individuals without lung cancer and were most frequent and intense in patients dying of lung cancer (Table 6 of this Chapter). Ex-cigarette smokers and pipe and cigar smokers yielded a higher frequency of such cellular changes than non-smokers but less than did current cigarette smokers. Thus, the histopathologic evidence derived from laboratory and clinical material support the cigarette smoking-lung cancer hypothesis.

CONSTITUTIONAL HYPOTHESIS

GENETIC CONSIDERATIONS.—Thus far in the evaluation, the Committee has considered whether the available data are consistent with the hypothesis that smoking causes cancer of the lung. The analysis must consider with equal attention the alternative hypothesis that both the smoking of cigarettes and cancer of the lung have a common cause which determines both that an individual shall become a smoker and also that he shall be predisposed to lung cancer. This has often been called the constitutional hypothesis. However, one should distinguish between the morphologic and physiologic characteristics of any individual due to a given environment and those characteristics (phenotype) that are due to an interaction of hereditary susceptibility and the environment.

The characteristics of individuals studied in relation to smoking have been numerous and varied. Some of them have been physical attributes such as physique or somatotype, height and weight and their ratios, masculinity, anthropometric variables, physiologic variables (heart rate, pulse pressure, blood pressure, cholesterol levels), and physical activity; others have been psychosocial (including personality) in character (Chapter 14). Cigarette smokers have been described as consuming more alcohol, drinking more black coffee, being more neurotic, engaging more often in athletics, and as being more likely to have at least one parent with hypertension or coronary disease (150, 214, 235). Many studies have been poorly designed and controlled, others have yielded contradictory findings, and still others, by admission of their authors, have included characteristics that could either have been acquired or have been produced by smoking. None of these constitutional attributes have been included in a prospective study of mortality from lung cancer fulfilling satisfactory epidemiological criteria, except for a breakdown by longevity of parents and grandparents in one study (159). The genetics of the characteristics themselves has not been determined, and adequate analysis of common genetic determinants in relation to the habit of smoking has not been attempted. No environmental determinants that would universally induce smoking and also produce the characteristics are evident (62) or have been proposed.

Fisher (118) has been foremost in calling attention to the possibility that cancer of the lung and the habit of smoking may be due to a common genotype. Selection of smokers then would automatically provide a population in which pulmonary cancer would appear on the basis of genetic susceptibility.Studies on the concordance of smoking in twins (122, 127, 281, 356) were used to support the hypothesis, since more monozygotic pairs have similar smoking habits than do dizygotic pairs. Although the data on the smoking habits of identical and fraternal twins raised apart are compatible with this hypothesis, the history of cancer in twins whose smoking habits are known has never been documented sufficiently to he useful in helping to resolve the question of whether the concept of the constitutional hypothesis is valid. Also information about the habits and medical history of other siblings, offspring, and parents is singularly scanty, and efforts to separate genetic factors from influences of the environment in such studies have been only rudimentary.

Although single genes may be involved in a few exceptional neoplastic and preneoplastic states such as retinoblastoma and precancerous colonic polyposis, genes for susceptibility to human cancer are usually multiple (48). Whether multiple genes for susceptibility may also be operating in the instance of cancer of the lung has not been established. The linkage (in a genetic sense) between multiple genes related to a habit (smoking) and a disease (lung cancer) in an heterogeneous population would require numerous coincidences with small probabilities. Also, in order to adhere to a consistent argument in explaining the reduced incidence of cancer of the lung in this group, it would be necessary to postulate another common genotype for those who smoke and subsequently terminate the habit. The argument becomes even more labored when multiple examples of identical genotypes for susceptibility to smoking and respective specific types of cancer are required by the hypothesis to explain the multiple types of cancer associated with smoking.

Since cancer of the lung occurs in both men and women who do not smoke, susceptibility genes acting alone or in combination with extrinsic or additional intrinsic factors can be effective without exposure to tobacco smoke. The occurrence of the disease, therefore, is not invariably linked to hypothetical genes responsible for the habit of smoking. Since susceptibility to cancer may be due to multiple genes with variable penetrance, and since the expression of these genes may change with environmental conditions, a minor portion of the cases of pulmonary cancer can be explained as the expression of genetic susceptibility in an environment excluding the habit of smoking.

Smoking then may add an extrinsic determinant which can increase the incidence of cancer of the lung beyond that which would otherwise prevail in the same population.

It should be emphasized that comparisons of lung cancer mortality in smokers, non-smokers and ex-smokers have been made on different populations. Thus, in considering the fact that the incidence of lung cancer appears to decrease when smoking is discontinued, it must be remembered that the population which can stop or does stop smoking may differ from that which continues. It is possible that the ability to terminate the habit may also be determined genetically.

In assessing the importance of a possible genetic influence in the etiology of lung cancer, it should be recalled that the great rise in lung cancer incidence in both men and women has occurred in recent decades. This points either to a change in the genic pool, or to the introduction of an agent into the environment, or a quantitative increase of an agent or agents capable of inducing this type of cancer. The genetic factors in man were evidently not strong enough to cause the development of many cases of lung cancer under environmental conditions which existed half a century ago. In terms of what is known about rates, pressures, and equilibria of human mutations the assumption that the genome of man could have changed gradually, simultaneously and identically in many countries during this century is almost inconceivable.

Smoking may be placed more properly in the role of an environmental determinant than as part of the phenotype of the pluripotential gene or genes, interacting with the environment and resulting in cancer of the lung.

Current evidence is compatible with the opinion that genetic factors play a minor role compared to the contribution of the smoking habit in the etiology of lung cancer today.

EPIDEMIOLOGICAL CONSIDERATIONS.—Although evidences for the constitutional hypothesis are, at present, either tenuous of actually lacking, the basic philosophical and logical prerequisites for this hypothesis are contradicted by a number of well-established observations (62) :

(1.) Lung Cancer Mortality.—Lung cancer mortality has been increasing in the last 50 years and much more in males than females. This increase could be due to either an environmental change or a mutation. Since an unchanging constitutional makeup cannot of itself explain the increase, we must postulate either that there are genetic differences which make some individuals sensitive to a new environmental factor (not tobacco), or that differences in constitutional makeup are not genetic but the result of differential exposure to some new factor that predisposes to lung cancer and creates the desire to smoke, or that the mutation has produced an increased susceptibility and a desire to smoke. For the first two postulates a new environmental factor, other than tobacco, is required. Such a factor, it must be remembered, must be correlated with lung cancer as highly as are cigarettes and also highly correlated with cigarette consumption. None has yet been found. In order to account for the magnitude of the lung cancer mortality increase, the third postulate would require a mutation rate which far exceeds any observed.

(2.) Tobacco Tars.—Tobacco tars have been found to be carcinogenic for experimental animals. Although carcinogenicity of tobacco tars has not been demonstrated in man, the constitutional hypothesis would require that they are not, and that the association with lung cancer in man of substances found to be carcinogenic for experimental animals is a coincidence.

(3.) Pipe and Cigar Smoking.—Pipe and cigar smoking appears to have a higher correlation with laryngeal and oral cancer than with lung cancer. The constitutional hypothesis would require that there shall be two constitutional makeups, one predisposing to cigarette smoking but not to pipe and cigar smoking and also to cancer of the lung; the other predisposing to tobacco consumption in any form and to cancer of the larynx and oral cavity but not to cancer of the lung. The alternative within this hypothesis would require that the special constitutional makeup predisposes to cigarette smoking and lung cancer, but that tobacco smoke, whether from cigarettes, cigars or pipes, is carcinogenic for the larynx and oral cavity but not for the lung. These requirements are unrealistic.

(4.) Ex-cigarette Smokers.—Ex-cigarette smokers have a lower lung-cancer mortality and a gradient is noted by length of time smoking has been discontinued and by the amount previously smoked. This would require complicated genetic interrelationships if the constitutional hypothesis were to be satisfied. A simpler hypothesis, which involves a causal relationship be-

tween smoking and lung cancer, but recognizes differences, defined or ill defined, between smokers and non-smokers may be stated as follows: There are factors in the individual acquired early (or genetic) which predispose to cigarette smoking, and cigarette smoking by direct action of smoke on the bronchial epithelium is a major factor in producing lung cancer in susceptible individuals.

A detailed discussion of the significances of the data on psycho-social, constitutional, and physical characteristics of smokers and non-smokers is presented later in this report (Chapters 14 and 15). The role of the genetic factor in carcinogenesis has been discussed earlier in this Chapter.

OTHER ETIOLOGIC FACTORS AND CONFOUNDING VARIABLES

Throughout this evaluation, it has been recognized that a causal hypothesis for the cigarette smoking-lung cancer relationship does not exclude other factors. This is attested to by the fact that a small but not insignificant percentage of cases of lung cancer does occur among non-smokers. Some estimates in retrospective studies and most of the prospective studies indicate that approximately 10 percent of the lung cancer cases are in non-smokers. Doll (78) has provided a higher estimate of 20 percent. Furthermore, the inability to account for the higher lung-cancer incidence in the lower economic classes entirely by disparities in smoking habits, which do exist, does imply other causal factors.

Several other possible etiologic factors which have been explored merit discussion. These include occupational hazards, urbanization or industrialization and air pollution, and previous illness.

(1.) Occupational Hazards.--In an extensive review of the literature on lung cancer in chromium and nickel workers and in uranium miners, Seltser (318) found the evidence for an excess of lung cancer mortality among chromate workers highly consistent. However, because of the smallness of the numbers involved, caution must be exercised in any calculation of the magnitude of the risk. Furthermore no evidence has been presented either for or against an excess risk of lung cancer among workers exposed to other chromium products or chromium mining. The evidence for an excess risk among nickel processing workers in refineries was even more consistent than for chromate workers. The lung cancer risk was five times greater among nickel processing workers than in other occupational groups in the same area (the risk for nasal cancer was 150 times higher). Among uranium miners an excess risk is apparent (360), and is greater than in certain other miners of similar ores without the high radioactivity component (361). Although the induction of lung cancer by radio nuclides is probable in man, the evidence is not as firm as in animals.

In addition, Doll has found a significant excess of lung cancer deaths among coal gas workers (81) and asbestos workers (77). In another review article, Doll (79) has added arsenic and hematite as suspects to the list, with isopropyl oil, beryllium, copper, and printing ink as possible risks.

The evidence for the possible role of arsenic as a factor in the etiology of lung cancer has been summarized by Hueper (178), and Buechley (45) has

recently suggested that it merits epidemiological investigation. The chief points of evidence cited include 1) the universality of arsenic in many ores and in the atmospheres in and near smelters; 2) the widespread use of arsenic as an insecticide and the consequent exposure of workers in insecticide manufacture, agricultural workers, and those handling or consuming crops with arsenic residues; and 3) reports of a relatively high incidence of lung cancers in people living around smelters processing arsenic-containing ores, and also in vineyard workers exposed to large amounts of arsenical pesticides and consuming large amounts of arsenic-contaminated beverages.

It is noteworthy that for the nickel and chromate material the lung cancer mortality is referrable to a high exposure period in the respective industries, a situation which probably does not prevail today. Of greater importance is the regrettable fact that in none of these occupational hazard studies were smoking histories obtained. Thus the contribution which smoking, as a contributory or etiologic factor, may have made to the lung cancer picture in these risk situations is unknown. However, the series of cases in non-smoking chromate workers is large enough to exclude the possibility that cancers of the lung in chromate workers develop only in those who smoke cigarettes. Nevertheless, it must be emphasized quite strongly that the population exposed to industrial carcinogens is relatively small and that these agents cannot account for the increasing lung cancer risk in the general population.

(2.) Urbanization, Industrialization, and Air Pollution.--The urban-rural differences in lung cancer mortality risk, though small and accounted for in part by differences in smoking habits (see section entitled Coherence of Association), nevertheless may have a residual which implies other etiologic factors in an urban environment. This has been the explanation offered in the studies by Stocks and Campbell (337) and Stocks (335) who noted a gradient among non-smokers, light cigarette smokers and pipe smokers by density of population but who found no gradient among heavy smokers. Less direct evidence was derived by Eastcott (101) and Dean (69, 71) who found higher lung cancer rates among migrants from Great Britain to New Zealand, South Africa and Australia. respectively. Their inferences were that these immigrants had had significant exposure to air pollution in England prior to coming to the Commonwealth countries. Unfortunately, these interpretations were untenable for there was no individual case-control information on tobacco consumption. A correction of method by Dean in a later study (70) did elicit smoking histories and revealed a marked influence of cigarette smoking but a significant though lesser factor of urbanization. Doll's study of non-smoking lung cancer cases (78) revealed no differences in risk among men and women and in residents of areas of different population density. His findings cannot be considered to be conclusive of a negative result, for density of population need not necessarily be highly correlated with pollution. In a more recent. as yet unpublished, paper by Stocks* a

*Stocks, P.: A Study of Tobacco Smoking, Air Pollution, Residential and Occupational Histories and Morality from Cancer of the Lung in Two Cities. Inter-regional Symposium on Criteria for Air Quality and Methods of Measurement, W.H.O., Geneva, Switzerland, August 6-12, 1963.

mathematical model embodying amount of smoking, age, air pollution measurements by specific carcinogenic constituents, proportion of life spent in country and town, and lung cancer mortality was applied to the data derived from Belfast and Dublin. The lung cancer death rates were found to be compatible with an hypothesis that in Belfast about two-thirds of the deaths of men resulted from cigarette smoking and one-third from air pollution by smoke and, in Dublin, 75 percent from cigarette smoking and 25 percent from air pollution. These data are not offered as proof but represent the approaches necessary for future research in the area of proportional contributions to lung cancer mortality. Such applications may be useful in determining the role of air pollution in such disparate lung cancer mortality rates between, for example, the United States and Great Britain when adjustments in smoking habits still do not eliminate the difference completely.

Two studies (147, 152) have also indicated that migration of rural people into urban areas subjects them to lung cancer risks greater than for lifetime urban residents. This effect is noted among non-smokers as well. The least that can be said is that the intensity of urbanization or industrialization may have a residual influence on lung cancer mortality.

(3.) Previous Respiratory Infections.--Relatively few soundly designed studies have tested the effect of prior respiratory disease, particularly infections, on the development of lung cancer.

Winternitz (371) called attention in 1920 to proliferative changes in cases of post-influenzal pneumonia similar to those seen in invasive, malignant neoplasms of the lung but this report stimulated relatively few epidemiologic observations. In the retrospective study of the smoking-lung cancer relationship by Doll and Hill (82) inquiry into a history of previous respiratory infections led to finding a significant excess of antecedent chronic bronchitis and pneumonia among lung cancer patients even when smoking class was controlled. However, because a collateral comparison with another control group of patients, for whom a lung cancer diagnosis was subsequently found to be in error, failed to reveal a difference, Doll and Hill concluded that either "chronic bronchitis and pneumonia predispose to a whole group of respiratory disorders . . or that patients with respiratory disorders recall previous chronic bronchitis and pneumonia more readily than do patients with diseases with other symptoms." However, almost simultaneously Beebe (20) investigated the relationship between mustard gas exposure, chronic bronchitis, pneumonia and influenza and lung cancer, and Case and Lea (53) between mustard gas exposure and/or chronic bronchitis and lung cancer. Smoking histories were controlled in these studies. Beebe found no evidence of an increased lung cancer risk with an antecedent history of influenzal pneumonia and primary pneumonia but there did appear a highly suggestive association between mustard gas exposure and lung cancer. No relationship between chronic bronchitis and lung cancer was noted. Case and Lea, however, interpreted their findings to mean a sequential relationship between mustard gas exposure, chronic bronchitis, and lung cancer. The lung cancer risk was doubled by pre-existing chronic bronchitis. Doll,

in a later review (76), however, indicated that since the smoking-lung cancer relationship is stronger than the chronic bronchitis-lung cancer relationship, chronic bronchitis is not a necessary intermediate pathogenetic process. The failure of the Beebe study to affirm the Case and Lea findings in regard to chromic bronchitis may lie in the problem of differences in British and American diagnoses of chronic bronchitis.

In an epidemiologic approach to other factors in lung cancer risks, Denoix et al. (72) studied 160 characteristics. Among other factors, much less strongly associated with lung cancer than smoking of cigarettes, they found a history of exposure to war gas and chronic bronchitis to predispose to lung cancer. The war gas component was strong enough to double the risk of lung cancer even with control on smoking class.

Thus, the observations on previous respiratory illness are too few in number to place any degree of assurance on a relationship, but the studies by Case and Lea and by Denoix et al. remain interesting.

(4.) Other Factors.--Numerous other factors, such as coffee drinking, alcohol consumption nutritional status, and beer drinking, have been studied and some associations with lung cancer have been found, but none of them does more than double the risk (and sometime these are noted to be associated with lung cancer via the smoking component) as compared to the 9- to 10-fold risk in average cigarette smokers and the 20+ fold risk in heavy smokers.

Conclusions

1. Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive. point in the same direction.

2. The risk of developing lung cancer increases with duration of smoking and the number of cigarettes smoked per day, and is diminished by discontinuing smoking.

3. The risk of developing cancer of the lung for the combined group of pipe smokers, cigar smokers. and pipe and cigar smokers is greater than in non-smokers, but much less than for cigarette smokers. The data are insufficient to warrant a conclusion for each group individually.

ORAL CANCER

Epidemiological Evidence

The suspicion of an association between use of tobacco and oral cancer dates back to the early 18th Century when Holland (176) first noted cancer of the lip among users of tobacco. In 1795, Soemmering (322) made the same observation. In the present era, additional clinical observations have been recorded. The investigators noted the proportions of users of the

various forms of tobacco among the various cases of oral cancer and found clues to a relationship. These observations lacked controls. Notable among these reports are the review by Haase (142) emphasizing location of the cancer of the lip and mouth according to where the pipe was held; the analysis by Ahlbom (1) by specific type of tobacco use in relation to site; and the work of Potter and Tully (280) which indicated an increase in risk of oral cancer with increase in smoking. From the first two studies mentioned (1, 142), it is immediately apparent that any reasonably meaningful study of the relationship between tobacco and oral cancer must take into account not only the specific sites (lip, cheek, gingiva, tongue, oropharynx, etc.) but also the precise form of tobacco use (pipes, cigars, cigarettes, chewing tobacco, snuff, etc.).

Of additional interest is the specialized use of tobacco as a component of betel nut quids in certain areas of the world; several observations suggest an association with oral cancer (66, 67, 269, 319). In contrast, observations of populations using betel nut quids without tobacco (104, 234, 367) in certain other areas of the world show no association of betel nut with oral cavity cancer.

More formalized case-control or retrospective studies varying in specific approach, in suitability of controls and in sample size have appeared between 1920 and the present (26, 41, 103, 202, 207, 221, 237, 245, 272, 301, 306, 314, 326, 355, 369, 385, 387, 388, 398). These studies are described in Table 10 which includes general smoking data, for the most part, on combinations of specific sites of oral cancer. A number of these investigations either did not separate the several sites of the oral cavity because of the small number of cases for each site or, upon separation into such sites, found the smoking classes too numerous for testing of significance (26, 221, 237, 388). Since associations with form of tobacco use varied according to smoking classes and, wherever possible, to specific sites (Table 10A), in this summary table, a statistically significant positive association is designated by a plus sign, whereas the lack of such an association is designated by a minus sign. A plus-minus sign indicates that there was some evidence of an association which was not, however, statistically significant.

It will immediately be noted that in 10 of 17 studies all oral sites were combined in an attempt to elicit an association with forms of tobacco-use (26, 202, 221, 237, 245, 272, 306, 314, 326, 388). Although eight of these showed positive association, they were so scattered among the several forms of tobacco use that little can be derived from them. Furthermore, distinctly specific site associations may be masked by such combinations. In examining the data for specific site localizations and forms of tobacco use, several associations become clarified.

It would appear that pipe smoking is associated with lip cancer in all six studies in which this site and form of tobacco use was analyzed (41, 103, 207, 301, 378, 385).

In one additional study (237) an association with pipe and cigars com-

TABLE 10.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity*

Investigator and year	Reference	Country	Sex	Cases		Controls		Collection of data
				Number	Method of selection	Number	Method of selection	
Broders 1920	(41)	U.S.A.	M F	526 11	Series of clinic patients with epithelioma of the lip. 80.5% tobacco users 75.1% smokers 0.9% cigarettes 24.0% chew 59.0% pipes 38.5% cigars	500	Series of clinic patients without epithelioma of the lip. 78.6% tobacco users 75.2% smokers 44.4% cigarettes 13.4% chew 28.6% pipes 44.0% cigars	Apparently by interview in the clinic.
Lombard and Doering 1928.	(221)	U.S.A.	M–F	217	Clinic patients with cancer of various sites. Site breakdown and smoking data not clear.	217	Clinic patients without cancer, matched by sex and age. Smoking data not clear.	Personal interview by investigators in clinics.
Bigelow and Lombard, 1933.	(26)	U.S.A.	M–F	(?)	Clinic and hospital patients, apparently several hundred. 14.2% non-users 36.4% excessive users (Table 111).	(?)	Patients without cancer, in comparable numbers. 26.5% non-users 24.0% excessive users (Table 111).	Personal interview in hospitals and clinics.
Ebenius 1943	(103)	Sweden	M F	439 33	Clinic patients with cancer of the lip. 79.7% tobacco users, M 57.6% tobacco users, F (all pipes) 61.8% pipes, M 47.4% chew or use snuff, M 12.9% cigars and cigarettes, M		Not defined. 68.7% tobacco users, M 1 to 2 %! tobacco users, F 22.9% pipes, M 60.7% chew or use snuff, M 32.5% cigars and cigarettes, M	
Levin et al. 1950	(207)	U.S.A.	M	143	Cancer institute patients with cancer of the lip. 84.5% smokers 45.3% cigarettes 48.1% pipes 26.5% cigars	51	Cancer institute patients with non-cancer diseases of same site. 74.0% smokers 43.0% cigarettes 30.7% pipes 34.9% cigars	Routine clinic interview.
Mills and Porter 1950	(237)	U.S.A.	M	124	Deaths from cancer of oral cavity in Cincinnati and Detroit, 1940–45 and 1942–46, respectively. 35.5% cigarettes only 54.8% pipes, cigars, or combinations	185	Sample of population of Columbus, Ohio, and in same proportion of color, sex, and age as in cases. 32.4% cigarettes only 29.7% pipes, cigars, or combinations.	From next of kin of deceased by mail questionnaire or by personal interview. Controls by house-to-house interview.

Moore et al. 1953	(245)	U.S.A.	M	112	Patients over 50 yrs. old since 1951 with cancer of oral cavity. 58.0% chew 42.0% pipes 38.4% cigars and cigarettes	38	Patients of same age groups with benign oral lesions or benign surgical conditions. 31.6% chew 47.4% pipes 52.6% cigars and cigarettes	Personal interview of controls; for cases, next-of-kin were visited or contacted by letter.
Sadowsky et al., 1953	(301)	U.S.A.	M	1,136	Hospital patients with oral and pharyngeal cancer, 1938–43. 42.3% cigarettes only 4.0% cigars only 17.8% pipes only 28.2% mixed	615	Patients with illness other than cancer. 53.3% cigarettes only 3.4% cigars only 7.0% pipes only 23.1% mixed	By trained lay interviewers.
Sanghvi et al., 1955	(306)	India	M F	657 81	Hospital patients with cancer of oral cavity and pharynx. 38.8% smoke and chew, M; 3.7% F 46.7% smoke only, M; 6.2% F 11.7% chew only, M; 64.2% F 2.7% neither, M; 25.9% F (Smoking is of bidis among both cases and controls.)	M 288 F 112	Hospital patients with diseases other than cancer. 24.0% smoke and chew, M; 0% F 50.0% smoke only, M; 6.3% F 8.7% chew only, M; 23.2% F 17.3% neither, M; 70.5% F	Personal history interview in hospital.
Ledermann 1955	(202)	France	M	240	Patients with cancer of oral cavity & pharynx. 4.6% non-smokers 23.4%>20 cigarettes per day	62	Patients with cancer of skin, bone, muscle. 17.2% non-smokers 18.6%>20 cigarettes per day	
Wynder et al., 1957	(378)	U.S.A.	M F	543 116	Patients with cancer of oral cavity 3% non-users, M; 47% F 20% cigars, M 11% pipes, M 8% mixed, M 17% chew, M 57% cigarettes, M; 53% F 29%>35 cigarettes per day, M 34%>16 cigarettes per day, F	M 207 F 232	Patients with cancer of other sites and benign diseases. 10% non-users, M; 70% F 13% cigars, M 6% pipes, M 8% mixed, M 8% chew, M 63% cigarettes, M; 30% F 17%>35 cigarettes per day, M 11%>16 cigarettes per day, F	Personal interviews in hospital or clinic.
Wilkins and Vogler 1957.	(369)	U.S.A.	M F	37 44	Clinic and hospital patients with cancer of gingiva. 32% chew or chew and smoke, M 20% smokers, M 52% use snuff, F 9% smokers, F		None.	Clinic and hospital histories.
Schwartz et al.	(314)	France	M	332	Hospital patients with cancer of oral cavity and pharynx. 16.4% non-smokers 62.7% cigarettes only 3.3% pipes only	608	Hospital patients with non-cancer illness and accident cases, matched by age. 23.4% non-smokers 58.2% cigarettes only 3.0% pipes only	Questioned about the same time by the same interviewer.

TABLE 10.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity*—Continued

Investigator and year	Reference	Country	Sex	Cases		Controls		Collection of data
				Number	Method of selection	Number	Method of selection	
Wynder et al. 1957	(388)	Cuba	M F	178 34	Hospital clinic patients with cancer of oral cavity and pharynx 4% non-smokers, M; 24% F 45% cigarettes predom., M; 62% F 33% cigars predom., M; 12% F	M 220 F 214	Patients in same clinics with non-malignant conditions, matched by sex and age. 16% non-smokers, M; 66% F 45% cigarettes predom., M; 27% F 22% cigars predom., M; 6% F	Personal questioning in clinic, all by 2 interviewers.
Wynder et al. 1957	(385)	Sweden	M F	115 140	Hospital patients with cancer of oral cavity and pharynx. 36.5% cigarettes, M 13.0% cigars, M 12.2% pipes, M 15.7% mixed, M	M 115 F 156	Patients in same hospital with cancer of sites other than oral, pharynx, larynx, lung, esophagus and breast. 36% cigarettes, M 9% cigars, M 16% pipes, M 13% mixed, M	Personal interview in hospital; and medical histories.
Peacock et al. 1960	(272)	U.S.A.	M F	25 20	Hospital patients with oral cancer 55.6% chewed or used snuff over 20 years.	M 74 F 72	Patients in same hospital without oral cancer and 117 male and 100 female randomly selected outpatients. 32.6% of first group, 43.3% of second group chewed or used snuff over 20 years.	Personal interviews.
Staszewski 1960	(327)	Poland	M	383	Male patients with oral cancer 5.7% non-smokers 72.8% "heavy" smoking index 72.3% cigarettes only 12.8% pipes and/or cigars	912	Male patients with other cancer and non-cancerous conditions. 17.3% non-smokers 49.0% "heavy" smoking index 60.5% cigarettes only 11.1% pipes and/or cigars	Personal interviews.
Vogler et al. 1962	(355)	U.S.A.	M F	188 92	Clinic patients with cancer of lip and oral cavity 32.9% chewers, M [2] 22.9% excessive chewers, M 72.0% snuff dippers, F 41.3% excessive snuff dippers, F 90% tobacco users, M + F	M 521 F 1,064	Patients of same clinic with other cancer or non-malignant conditions. 6.1% snuff dippers, F [2] 56% tobacco users, M + F	Personal interviews in clinic.

[1] Estimate of prevalence o use.
[2] Due to varying tabular treatment of the data, the percentages of tobacco users are not all based on the same numbers of cases.

TABLE 10A.—*Summary of results of retrospective studies of smoking by type and oral cancer of detailed sites* [1]

Investigator and reference	Cigarettes	Pipes	Cigars	Chewing	Miscellaneous
Broders (41)	(Lip)−	(Lip)+	(Lip)−	(Lip)+.	
Lombard and Doering (221).		(Oral)+			
Bigelow and Lombard (26)					(All forms combined—oral)+
Ebenius (103)	(Lip)− [2]	(Lip)+		(Lip)−.	
Levin et al. (207)	(Lip)−	(Lip)+	(Lip)±.		
Mills and Porter (237)	(Oral)±				(Pipes and cigars combined—oral)+.
Moore et al. (245)	(Lip, mouth)− [3]	(Lip, mouth)−		(Lip, mouth)+	(Snuff—lip, mouth)+.
Sadowsky et al. (301)	(Lip, tongue, other oral, pharynx)−.	(Lip, tongue, other oral)+	(Tongue, other oral)+.		
Sanghvi et al. (306)	(Oropharynx)+ [3]			(Oral)+	(If smoke and chew—base of tongue, hypopharynx)+.
Ledermann (202)	(Oral)+.				
Wynder et al. (378)	±M, +F (Floor of mouth).	(Each site except tongue)+	(Each site)+	(Gingiva, lip)±.	
Schwartz et al. (314)	(Pharynx)+ [4]	(Oral)−.			
Wynder et al. (368)	M−, F+ (Oral and pharynx).	(Lip)+	M+, F+ (oral and pharynx).		
Wynder et al. (385)	(Pharynx)+, (Other sites)−		(Tongue, gingiva, pharynx)+.		(Pipes, and cigars combined—tongue)+.
Peacock et al. (272)				(Oral)+ [5]	(Snuff—oral)+.[5]
Staszewski (326)	(Lip, oral cavity)+				(Pipes and cigars combined—lip, oral cavity)±.
Vogler et al. (355)					(All forms combined)+, F+ (snuff—lip and buccal cavity in both cases).

[1] + = Significant association.
− = Association absent or not significant.
± = Association of doubtful significance.
[2] Cigarettes and cigars.
[3] Bidis.
[4] Includes cigarettes and other.
[5] Only in individuals of low economic status and over 60 years old.

bined was noted. Among four studies of lip cancer the chewing of tobacco and / or snuff was found to be associated in two of them (41, 245).

There is some indication of an association of tongue cancer with cigar smoking in three studies (301, 378, 385) and in one of these (385) with pipe and cigar smoking combined. In two studies an association of gingival cancer with cigar smoking was demonstrated (378, 385); in one of these (378) an association also noted with pipe smoking, and a suggestion of an association with chewing of tobacco.

Pharyngeal cancer was considered as a separate site in four studies (301, 306, 378, 385). An association with cigarette smoking was noted in two out of three (306, 385); with cigars in two (378, 385); and with pipe in one (378).

Among the better studies in which the sample sizes were large and controls adequate, one deserves special mention (301). In this investigation by Sadowsky and others, it was possible to establish gradients for lip cancer by number of pipefuls smoked a day, for tongue cancer by amount of tobacco in pipes and cigars combined, and for other oral cavity cancers by number of pipefuls. No gradient by amount smoked was noted for cigarettes.

The seven prospective studies have yielded 152 cases of oral cavity cancer associated with cigarette smoking, with an adjusted expectancy of 37.0 cases giving a weighted mean mortality ratio of 4.1. This is the third highest mortality ratio of cigarette smokers to non-smokers among the several specific types of cancer deaths and the fourth highest among all causes of death associated with cigarette smoking. The mortality ratios ranged from 1.0 in the Dunn, Linden, Breslow occupational study (96), in which only seven cases have thus far been observed, to 9.2 in the current Hammond study (157). (See Table 1 of this chapter.)

For cigar and pipe smokers, oral cancer has the highest mortality ratio, 3.3, of all causes of death, exceeding cancer of the esophagus, larynx and lung. Recently calculated data from six of the prospective studies (excluding the current Hammond study) show a slight gradient in the mean mortality ratios for cigarette smokers of more than a pack a day as compared to smokers of one pack or less. Estimate of gradients by amount of smoking of pipe and/or cigars, by duration of smoking and by discontinuance are not yet available, because of the relatively smaller number of deaths from oral cancer.

Inasmuch as the incidence of female oral cancer is markedly lower than in males, data on these variables for the female, to be derived from the current Hammond study, will require an inordinately prolonged observation period.

Carcinogenesis

Cigarette smoke and cigarette smoke condensates have failed to produce cancer when applied to the oral cavity of mice (75, 177, 240) and rabbits (312) or to the palate of hamsters (194, 303). Exposure of the hamster cheek pouch to cigarette tar, snuff, or tobacco also failed to induce cancer

(95, 194, 243, 244, 245, 246, 271, 272, 303, 303a). Leukoplakia was reported to have been induced by the injection of tobacco smoke condensates into the gingiva of rabbits (296).

The oral mucosa appears to be resistant in general to cancer induction even when highly active carcinogens such as benzo(a)pyrene (95, 194, 209, 243, 244, 245, 246, 271, 272, 296, 303) are applied. Mechanical factors, such as secretion of saliva, interfere with the retention of carcinogenic agents. Saliva may also play a chemical role in modifying the action of carcinogenic agents on the tissues of the oral cavity and the pharynx. The only positive results with carcinogens have been obtained with benzo(a)pyrene, 20-methylcholanthrene, and 9,10-dimethyl-1,2-benzanthracene applied to the cheek pouch of the hamster (244, 303, 343). The cheek pouch, however, lacks salivary glands, and its structure and function differ from those of the oral mucosa.

Pathology

There is a strong clinical impression linking the occurrence of leukoplakia of the mouth with the use of tobacco in its various forms (201) However, in almost all the studies, the diagnosis of leukoplakia was made without histopathologic examination. It is difficult to distinguish clinically between hyperplasia of the surface epithelium with keratinization (termed *pachyderma oralis)* and "true" *leukoplakia,* which resembles microscopically senile keratosis, a preneoplastic lesion of the skin, showing atypical changes and mitotic figures, in addition to hyperplasia.

In a study of the tissue changes in the palate of women in a part of India where the burning end of a cigar is held inside the mouth, Reddy and Rao (284) found ulceration, increased pigmentation of the epithelium of the palate and leukoplakia. Many of these women develop cancer at the same site. The carcinomas found are epidermoid and are frequeutly surrounded by an area of leukoplakia which sometimes shows changes characteristic of carcinoma-in-situ. Leukoplakia is a common finding in patients with multiple oral carcinomas, the majority of whom use tobacco (241). A histopathologic study of lesions in the oral mucosa in betel nut-tobacco chewers in Malaya showed frequent epithelial hyperplasia with atypical changes and papilloma formation (233). These lesions were considered to be frequent sites for the subsequent development of cancer. An association between leukoplakia and oral cancer has been noted by other investigators in studies on individuals with the habit of dipping snuff (179, 200).

Although these results do not warrant any conclusion by themselves, they are consistent with the suggestion that oral cancer is frequently preceded by characteristic premalignant changes and that these have a relationship to the use of tobacco.

Evaluation

Because of the diversity of sites involved in the category oral cancer and the need to delineate forms of tobacco use in each of them, the number of retrospective studies is inadequate to furnish sufficient material for a

judgment of *consistency* of the association except for cancer of the lip and pipe smoking.

Inasmuch as only one retrospective study (301) had large enough numbers of cases to derive the relative risks for specific site associations, reliance for *strength* of the association must be placed on the prospective studies. Since, in turn, the numbers of deaths from cancer of these sites so far have been small, only a combination of such sites could be analyzed for relative risk determinations. Five of the seven studies show reasonably high relative risk ratios for cigarette smokers and for cigar and pipe smokers.

Specificity of the association cannot be said to be as high as that noted for lung cancer. The prospective studies provide no information as to specific localizations within the oral cavity. Sadowsky et al. (301) showed an association of pipe smoking with cancer of the lip and of pipe and cigar smoking with cancer of the tongue.

Data are presently inadequate for a reliable assessment of the *coherence* of the association. However, it should be noted that the prospective studies provide a definite suggestion that a gradient of risk by amount smoked does exist for oral cancer and that in one large retrospective study (301) prevalence rates for every specific age group of smokers was consistently in excess over non-smokers.

It has been noted that during the past 30 years cancer of the oral cavity and pharynx has declined, primarily because of a decrease in lip cancer among males (130). Cancer of the lip has never been an important localization for females and the rates in females have remained fairly constant.

In males pipe smoking has decreased markedly in the United States during the past 30 years, so that the decline in lip cancer among males is not necessarily incompatible with a strong association between cancer of the lip and pipe smoking.

Furthermore, other probable factors in the production of oral cavity cancer such as mouth hygiene, nutrition, and particularly alcohol consumption have not remained stable. In two studies (314, 378) alcohol consumption is clearly also associated with oral cancer and in one (378) evidence is presented for independent operation of this factor.

The problem of heat from burning tobacco has not been investigated, as far as could be determined. It is of interest that cancer of the palate has been associated with smoking of cigars with the lighted end in the mouth (186). The heat factor should be kept in mind with respect to the excess of lip cancers among the cigar and pipe smokers.

Although cancer of the oral cavity has not been produced experimentally by the exposure of animals to tobacco smoke, it has occurred following repeated applications of benzo(a)pyrene and other hydrocarbons to the cheek pouch of the hamster.

The relationship of leukoplakia to tobacco use has been described earlier.

Conclusions

1. The causal relationship of the smoking of pipes to the development of cancer of the lip appears to be established.

2. Although there are suggestions of relationships between cancer of other specific sites of the oral cavity and the several forms of tobacco use, their causal implications cannot at present be stated.

LARYNGEAL CANCER

Epidemiologic Evidence

RETROSPECTIVE STUDIES

The possible association between tobacco smoking and laryngeal cancer received some attention in studies as early as 1937 (1, 185). Ahlbom noted a marked association between cigar and cigarette smoking and cancers of the pharynx, larynx and esophagus, but because of the small sample size, the three sites as defined were grouped together (1). The Kennaways calculated standardized mortality ratios for various occupational groups (against the age-specific mortality rates for the general population of England and Wales for 1921-32) and found barmen, cellarmen, and tobacconists to have significantly higher ratios (185). This latter study was repeated in 1947 and again the tobacconists and their assistants were noted to have an excess mortality for cancer of the larynx (184). It is difficult to attach much importance to these studies though they contain clues which should be investigated.

The earliest controlled study, retrospective in approach, was that of Schrek and co-workers (311) in 1950. Their very carefully analyzed data showed an association between smoking and cancer of the larynx but the evidence is not firm, for the association was found in only one out of four age groups, perhaps because of the small number of cases in the study sample. There then followed nine additional retrospective studies, two more in the United States (301, 376) and one each in Czechoslovakia (353), Germany (30), France (314), Sweden (385), Cuba (388), India (100), and Poland (327) (Table 11). These were stimulated in part by the retrospective studies of lung cancer and the general prospective studies.

Most of the studies (30, 100, 301, 311, 314, 327, 376, 385, 388) show a stronger association between cigarette smoking and laryngeal cancer than for other forms of tobacco use but one of the studies shows a borderline relationship with cigar smoking (385). Wynder et al. (376) also distinguished between intrinsic and extrinsic primary laryngeal cancers. It is of further interest that an excess risk of laryngeal cancer among cigar and pipe smokers in this study could be attributed to the extrinsic laryngeal cancer group. One study disclosed a relationship between laryngeal cancer and the combined smoking of cigarettes, pipes and cigars, as well as with cigarette smoking alone (301). In another (376) there is an impression that cigar and pipe smoking is more closely associated with cancers of the larynx than with cancer of the lung. A gradient of risk with amount smoked was demonstrated in two studies (301, 376) and suggested in four others (30, 311, 314, 327). In the study by Sadowsky et al., this gradient was noted not only for cigarette smokers but for pipe smokers and combination smokers as well.

TABLE 11.—*Outline of retrospective studies of tobacco use and cancer of the larynx*

Investigator and year	Reference	Country	Sex	Cases		Controls		Collection of data
				Number	Method of selection	Number	Method of selection	
Schrek et al. 1950	(311)	U.S.A.	M	73	Referrals from V.A. hospitals in "entire midwest" to V.A. Cancer Center, Hines, Illinois, during 1942–44: patients with larynx-pharynx tumors clinically or histologically diagnosed. 13.7% non-smokers 79.5% cigarettes 3.7% cigars 6.8% pipes	522	From same set of referrals, patients with tumors other than lip, lung, larynx-pharynx. 23.9% non-smokers 59.2% cigarettes 10.0% cigars 11.5% pipes	Random sample of 5003 admissions; questionnaires from Hines referrals for 1942–44; records included smoking history.
Valko 1952	(353)	Czechoslovakia.	M–F	226	Clinic patients with cancer of the larynx. 83.2% cigarettes 4.4% cigars 10.6% pipes 7.5% non-smokers	108	Clinic patients of same age group with other diagnoses. 22.2% non-smokers	Medical history and questionnaire in clinic.
Sadowsky et al. (1953)	(301)	U.S.A.	M	273	Admissions to hospitals in N.Y.C. Missouri, New Orleans, Chicago: patients with diagnosed laryngeal tumors, 1938–1943. 4.0% non-smokers 60.1% cigarettes only 2.2% cigars only 4.8% pipe only 28.9% some combination	615	From same set of admissions: patients with illnesses other than cancer. 13.2% non-smokers 53.3% cigarettes only 3.4% cigars only 7.0% pipe only 23.1% some combination	Sample of 2605 out of 2847 interviews (including smoking history) by trained lay interviewers.
Blümlein 1955	(30)	Germany	M	241	Clinic patients with cancer of the larynx. 0.8% non-smokers 79.3% heavy smokers 95.0% inhalers	200	Patients with no laryngeal disease. 18.0% non-smokers 4.3% heavy smokers 17.0% inhalers	Personal history taken in clinic.
Wynder et al. 1956	(376)	U.S.A.	M	209	Inpatients Memorial Cancer Research Center during 1952 to 1954, with benign or malignant epidermoid tumors of larynx. 0.5% non-smokers 86.0% cigarettes 7.5% cigars 5.0% pipes 1.0% cigars/pipes	209	Patients with other than epidermoid cancer, individually matched controls in same institutions. 10.5% non-smokers 73.7% cigarettes 10.1% cigars 3.8% pipe 1.9% cigars/pipes	Trained lay interviewers.

		India	M	132	Laryngeal cancer patients at Tata Memorial Hospital, 1952–1954. 13.6% non-smokers 78.8% bidis 5.3% cigarettes 1.5% hookah 0.8% chilum	132	Controls individually matched as for U.S.A. data above. 30.3% non-smokers 62.1% bidis 4.5% cigarettes 0.8% hookah 2.3% chilum	Interviews for smoking and medical histories.
Schwartz et al. 1957.	(314)	France	M	121	Patients hospitalized from 1954 through 1956 with laryngeal cancer, in Paris and other large cities. 96% smokers 58% inhalers 44% roll their own cigarettes	242	Same time and sources; patients hospitalized for non-cancerous conditions or trauma. 84% smokers 47% inhalers 31% roll their own cigarettes	Cases and controls individually matched within institutions; each member of a set questioned by the same trained lay interviewer.
Wynder et al. 1957----	(385)	Sweden	M–F	63	Patients at Radiumhemmet with squamous-cell cancer of larynx, from 1952 through 1955. Males: 5% non-smokers 47% cigarettes 17% cigars 15% pipes 17% mixed	271	Patients from same source and time, with cancer other than squamous-cell of larynx. Males: 24% non-smokers 36% cigarettes 9% cigars 16% pipes 13% mixed	By trained lay interviewers in hospital.
Wynder et al. 1958.	(388)	Cuba	M F	142 32	Clinic patients in Havana during 1956, 57, with histologically diagnosed epidermoid cancer of larynx. 1% non-smokers, M; 13% F 62% cigarettes, M; 72% F 20% cigars, M; 6% F 1% pipes, M 16% mixed, M; 9% F	M 220 F 214	Same source and time; apparently patients with cancers other than larynx, lung, or oral cavity, matched for age. 16% non-smokers, M; 66% F 45% cigarettes, M; 27% F 22% cigars, M; 6% F 1% pipes, M 16% mixed, M; 0% F	Interview of patients in clinic.
Dutta-Choudhuri et al. 1959.	(100)	India	M–F	582	Patients in Calcutta cancer hospital during 1950–54, with laryngeal tumor diagnosed and confirmed by biopsy or smear. 14.1% non-users 77.8% cigarettes or bidi 3.1% chew 5.0% both	288	Not specified. 41.7% non-users 52.1% cigarettes or bidi 3.8% chew 2.4% both	Tobacco histories obtained during 1951–54, apparently by interview.

TABLE 11.—*Outline of retrospective studies of tobacco use and cancer of the larynx*—Continued

Investigator and year	Reference	Country	Sex	Cases		Controls		Collection of data
				Number	Method of selection	Number	Method of selection	
Staszewski 1960.	(327)	Poland	M F	207 13	Patients admitted to chronic disease hospital during 1957 & 1958 with histologically confirmed squamous-cell carcinoma of the larynx. 0.5% non-smokers 87.9% cigarettes only 1.9% pipes and/or cigars 88.4% "heavy smokers" 96.1% inhalers 30.8% smoke, F	M 912 F 1813	Patients admitted during 1957 & 1958 to chronic disease center for cancerous and non-cancerous conditions presumably not related to tobacco consumption. 17.3% non-smokers 60.5% cigarettes only 11.1% pipes and/or cigars 49.0% "heavy smokers" 56.8% inhalers 8.4% smoke, F	Author interviewed patients suspected of lung cancer for smoking history and background.

A combination group of lung and laryngeal cancer cases was also included by Wynder et al. (376) and relative risks for lung cancer as well as laryngeal cancer among the several smoking categories were calculated. It is of interest that the risks attending the several categories of amounts of cigarettes smoked were similar for both lung and laryngeal cancer, but the risk of laryngeal cancer among cigar and pipe smokers was 2.5 times that for lung cancer.

Four of the retrospective studies concerned themselves with inhalation practices and a significant association between inhalation of cigarette smoke and laryngeal cancer was noted in three of them (30, 314, 327). The fourth study by Wynder et al. (376) found an association with inhalation among light cigarette smokers and among pipe and cigar smokers.

For both whites and non-whites the male-to-female age-adjusted sex ratios in laryngeal cancer are higher than for any other site common to both sexes (130). Despite the fact that the female case material is exceedingly sparse, at least two studies concerned themselves with laryngeal cancer in the female (377, 388). The material in one study was adequate to establish an association with cigarette smoking (388) whereas in the other only a suggestion was elicited in view of the paucity of the material (377).

Wynder and co-workers (387) in their study of Seventh Day Adventists noted that cancer of the larynx was an extremely uncommon reason for admission to a hospital and that this type of cancer was very infrequent among all cancer admissions. Smoking and drinking among adherents of this religious sect are uncommon.

PROSPECTIVE STUDIES

In the seven prospective studies previously described, laryngeal cancer has in each one of them been observed among smokers in frequencies in excess of the expected. Although in four of these studies (25, 84, 96, 97) the number of observed cases is so small as to weaken the stability of any calculable ratios, in the three major studies, the number of observed cases among cigarette smokers is reasonably large and yields ratios of 3.7 [current Hammond study (157)], 5.8 [Dorn (88)], and 13.1 [Hammond and Horn (163)]. A summation of all seven studies yields a mean mortality ratio of 5.4 (Table 1) for cigarette smokers. For five studies in which laryngeal cancer cases were associated with cigar and pipe smoking, the mean mortality ratio was 2.8. However, this was calculated from only nine cases observed and 3.2 expected (Table 24, Chapter 8).

None of the studies currently in progress has yielded a sufficient number of cases of laryngeal cancer to permit analysis of smoking class categories by inhalation practices, duration of smoking, and age started smoking. However, the recently calculated material from six prospective studies (Table 23, Chapter 8) shows a gradient of risk ratios from 5.3 for smokers of one pack or less of cigarettes per day to 7.5 for smokers of more than a pack per day. Because of the relatively low yield of cancers of this site, the current prospective studies (25, 84, 88, 96, 97, 157) will have to continue for a considerable length of time to provide answers to the other components of the problem.

Carcinogenesis

So far as known, no attempts to induce carcinoma of the larynx by tobacco smoke or smoke condensates have been reported.

Pathology

For information about histological changes in the larynx of smokers, see Chapter 10, Non-Neoplastic Respiratory Diseases.

Evaluation of the Evidence

The 10 retrospective studies have a high degree of *consistency* despite the weakness of the control selections in one or two of them. A sufficient number of these studies have an adequate sample size for categorization of type of smoking and these all show consistency in designating cigarette smoking as the significant associative class. The fact that each of the prospective studies yielded an excess of cases among cigarette smokers over the number expected from the incidence among non-smokers adds to the level of consistency noted. The calculations for cigarette smoking alone, as well as for the combination of cigarettes, pipes, and cigars, were almost identical to those in the prospective studies.

The relative *strength* of the association as measured by the specific mortality ratio (as an average of combined experiences) is admittedly not as high as that noted for lung cancer, but two of the three major prospective studies with adequate case loads indicate that the real value of the relative risk may approach that for lung cancer. As has been discussed in the section on lung cancer, the implication of a lower relative risk is that other factors of etiologic significance may be independently associated with the disease. That this may be true for laryngeal cancer, as it seems to be for oral cancer, is reasonable because alcohol consumption, though frequently associated with heavy smoking, appears to be associated with laryngeal cancer independently from smoking (376, 377).

As with lung cancer a dose-effect of smoking is also demonstrable. The majority of the retrospective studies have shown a greater association with heavy smoking and in two of them gradients with increasing amounts of tobacco consumed have been elicited. The prospective studies (Chapter 8, Table 21) also suggest a gradient although the numbers of deaths are small. Inhalation, a crude indicator of exposure, has also been noted as being asssociated with laryngeal cancer in each of the studies in which such analyses were attempted. The parallelism with lung cancer, though not as complete because of a smaller amount of material, is remarkable.

In an assessment of the coherence of the association between smoking and laryngeal cancer with the facts of the natural history and biology of the disease an approach similar to that utilized in the lung cancer analysis can be helpful.

TIME TRENDS

Although laryngeal cancer mortality has increased somewhat over the past three decades, the increase has been much less than that for lung cancer

mortality. In this regard it has also been mentioned that in at least one detailed study (376) the laryngeal cancer risk for cigarette smokers, irrespective of amount smoked, seems to be equal to that for pipe and cigar smokers (as a combined group). Furthermore, while the per capita consumption of cigarettes has risen, the consumption of pipe and cigar tobacco has declined. In addition, there is no evidence or reason to assume that the susceptibility of the larynx for cancer is equal to that of the bronchus. Finally, evidence has also been presented (stemming from the implications of lower mortality ratios of smokers to non-smokers) that other factors may play a significant role in the production of laryngeal cancer, such as alcohol and inadequate nutrition (376). Thus a diminution of such other factors in time could well have counterbalanced, in great part, a rise which could have attended increased cigarette consumption.

Tobacco chewing has also declined to such a great extent in this country that adequate case material among chewers is not available for analysis. However, evidence derived from studies among betel nut chewers in India indicates that even among smokers of cigarettes, cigars, pipes or bidis* the addition of tobacco to the material chewed is associated with an even greater risk of laryngeal cancer (100, 376). The evidence from the retrospective and prospective studies is compatible with the small rise in laryngeal cancer incidence observed.

SEX DIFFERENTIAL IN MORTALITY

As has been noted in the discussion of lung cancer, the much later advent of cigarette smoking among females would be compatible with their lower laryngeal cancer mortality rates. Furthermore, the negligible degree of pipe and cigar smoking and tobacco chewing among females would not only be compatible with a significantly lower risk of cancer of the larynx among them today as compared to males (WM:WF=10.8) but also with a lower sex ratio 30 years ago (WM:WF=6.3) (130). Assuming a reasonable induction period, the mortality rates 30 years ago could have been a reflection of the much lower consumption of tobacco even among males between 1900-1910 (239).

One cannot overlook the role of alcohol consumption in this differential. The greater alcohol consumption among males and a strong association between laryngeal cancer and alcohol consumption (376, 377) must he considered as contributing to the excess ratio of male to female laryngeal cancer mortality.

The role of inherent sex differences (e.g., hormonal, laryngeal anatomy) as determinants in the difference in mortality related to smoking cannot be fully evaluated from the limited information available.

LOCALIZATION OF LESIONS

Two studies have dealt analytically with laryngeal cancer from the stand. point of specific localization, i.e., extrinsic vs. intrinsic laryngeal cancer (327, 376). (Most laryngeal cancers designated as extrinsic arise in the larynx proper; about 30 percent designated as extrinsic arise in adjacent

*Bidi (variant of biri)--a locally made cigarette of tobacco Flakes rolled in the dried leaf of a variety of bauhinia (306).

structures such as the epiglottis, its valleculae and on the arytenoid folds.) In only one of these studies (376) were the data analyzed in sufficient detail to permit tentative interpretation. It should first be noted that intrinsic laryngeal cancer was more often associated with cigarette smoking, whereas a higher percentage of pipe and/or cigar smokers was found among extrinsic than among intrinsic cancers. Secondly, in both the United States and the Indian data referred to by Wynder, chewing of tobacco seems to be associated with a higher risk for the extrinsic type, implying that tobacco juice makes contact readily with such extrinsic structures as the epiglottis (37.6 percent of the extrinsic cancers were in this location). Finally, males predominate in intrinsic cancers of the larynx, whereas the ratio for extrinsic cancers, though lower, still shows an excess for the male. Thus far, the tobacco smoking and chewing patterns of males vs. females are compatible with the data on localization differences between the sexes. Extrinsic laryngeal cancer is relatively more common among rural than urban females. This evidence was presented by Wynder as indicating that some other factor which does not influence intrinsic lesions is operating. From some suggestive data he proposed dietary deficiency as a plausible explanation and cited the Swedish experience (385) as indicating the possibility of an iron-vitamin B complex deficiency. This remains to be adequately tested.

In any event, the male excess of cigarette smoking and the inhalation factor are compatible with the male preponderance of the intrinsic type of laryngeal cancer. Pipe and cigar smoking is also not devoid of some unconscious inhaling, at least to the level of the larynx. Furthermore, the more common findings of pipe and cigar smoking among cases of extrinsic laryngeal cancer are compatible with exposure to tobacco juice from this form of smoking. And, finally, the obvious exposure to such juice from tobacco chewing is compatible with the preponderance of extrinsic types among such users of tobacco.

Conclusion

Evaluation of the evidence leads to the judgment that cigarette smoking is a significant factor in the causation of laryngeal cancer in the male.

ESOPHAGEAL CANCER

Epidemiologic Evidence

RETROSPECTIVE STUDIES

As with cancers of other sites, clinical impressions of an association between smoking and esophageal cancer led to more or less controlled studies of the two variables as early as in 1937. Ahlbom (1) studied a group of patients with cancers of the pharynx, larynx, and esophagus and found an excess frequency of cigarette and cigar smokers among the combined group.

The first controlled retrospective study directed specifically to the esophagus was by Sadowsky et al. (301) published in 1953, the data for which were collected in the period 1938-43. These investigators found associa-

tions with cigarette and with cigar smoking but only the cigarette smoking relationship was noted to be statistically significant.

Since then there have been six other retrospective studies (306, 315, 325, 329, 374, 385) (Tables 12 and 13). It should he noted, however, that one of these (329) is an autopsy series with no reliable data on smoking histories. Among the five remaining studies with better data collection methods, significantly excess frequencies of tobacco smoking among esophageal cancer cases were noted in two (315, 325) excess frequencies of cigarette smoking were noted in two others (374, 385) but in only one of these (374) was the excess statistically significant. Cigar smoking and pipe smoking were implicated separately in these same two studies but again the excesses for each were statistically significant in only one study (374). In this latter study a significant association with tobacco chewing was also found. A portion of this same study was devoted to analyses of data collected in India. The Indian data should not be given the same weight as the others, since only 10 percent of the male cases and 4 percent of the female cases were histologically confirmed. It is of interest, however, that an association between tobacco smoking and esophageal cancer was observed.

The remaining study in this group is that of Sanghvi et al. (306) who found no significant associations with tobacco chewing alone and with cigarette and bidi smoking alone, but found a significant association for the combination of smoking and tobacco chewing.

Several of the studies were concerned with the amounts of tobacco smoked. The Swedish study by Wynder and co-workers (385) which had demonstrated excess frequencies of cigarette and cigar smokers among the esophageal cancer cases not to be statistically significant, showed a significant excess of amount of tobacco smoked among the cancer cases. A later study by Wynder and Bross (374) found significant excesses of heavy smokers among both male and female esophageal cancer cases. Staszewski (325) found a highly significant excess of heavy smokers among the cases in his Polish study. Schwartz and his co-workers (315) in the most extensive study of all, found significantly more smokers among cases than among controls. However, the difference in daily amount of cigarettes smoked was not significant.

A refinement of the data in two studies (301, 374) by classes of number of cigarettes smoked daily showed a gradient of increasing risks for esophageal cancer in both.

Inhalation practices were explored in two of the retrospective studies (315, 325). In neither of them was a significant difference found in percentage of inhalers between cases and controls.

Relative risk ratios were calculated from the data available in each of the retrospective studies (Table 13). The relative risks for all smokers in these studies ranged from 2.1 to 4.0 for American males and 2.0 to 4.1 for American females. Data were available for calculation of relative risks with regard to heavy smoking in only two of the studies (325, 374). The Polish data revealed a relative risk ratio of 16:1 for heavy smokers as compared with non-smokers, whereas the latest Wynder study revealed ratios paradoxically lower for heavy smokers than for the category “all smokers.”

In view of previous studies which had revealed an association between esophageal cancer and alcohol consumption, Wynder and Bross (374) tested

TABLE 12.—*Summary of methods used in retrospective studies of tobacco use and cancer of the esophagus*

Investigator, year, and reference	Country	Sex	Cases		Controls		Collection of data
			Number	Method of selection	Number	Method of selection	
Sadowsky et al. 1953 (301)	U.S.A.	M	104	White patients admitted during 1938–43 to selected hospitals in N.Y. City, Missouri, New Orleans, and Chicago.	615	White patients with illnesses other than cancer admitted to same group of hospitals during same period.	(1) Obtained by 4 especially trained lay interviewers. (2) 242 records out of a total of 2,847 excluded because of incomplete or questionable smoking histories.
Sanghvi et al. 1955 (306)	India	M	73	Consecutive clinic admissions to Tata Memorial Hospital, Bombay.	(1) 288 (2) 107	Consecutive clinic admissions of patients without cancer. Consecutive admissions of patients with cancers other than intraoral or esophagus.	By means of 'detailed questionary'. No other details given.
Steiner 1956 (329)	U.S.A.	M+F	116	Consecutive cases studied at autopsy in University of Chicago Dept. of Pathology during 1901–1954.	464	Autopsy cases comprising: 116 stomach cancer 116 lung cancer 116 malignant lymphatic dis. 116 cases without any malignant neoplasm. Matched by age, sex, race and year of autopsy.	Not clear how smoking histories were obtained—from hospital records, probably, which indicates they may be inadequate.
Wynder et al. 1957 (385)	Sweden	M	39	Patients admitted to Radiumhemmet, Stockholm during 1952–1955.	115	Patients admitted to same hospital with cancer of skin, and head and neck region other than squamous cell cancer, leukemia, colon, other sites. No matching.	
Staszewski 1960 (326, 327)	Poland	M	24	Patients admitted to Oncological Institute during 1957–59.	912	Other patients sent to Institute with symptoms probably not etiologically connected either with smoking or with diseases of esophagus, stomach or duodenum.	No details given on method of data collection. No age adjustment or matching. Average age of cancer patients=60.5 and of controls=53.
Schwartz et al. 1961 (315)	France	M	362	Admissions to hospitals in Paris and a few large provincial cities since 1954.	362	Healthy individuals admitted to same hospital because of work or traffic accidents—matched by 5 yr. age group and time of admission.	Interviewed by team of special interviewers who interviewed the largest proportion possible of all cancer patients. Cases and matched controls interviewed by same person.

Wynder and Bross, 1961 (374).	U.S.A.	M	150	Cancer patients seen in Memorial Hospital, N.Y.C. and Kingsbridge and Brooklyn VA Hospitals during 1950-59 (86% white).	150	Patients seen in same hospitals during same time period with other tumors. 64%-malignant tumors; 36%-benign conditions. Matched by age with cancer patients	Data collected by trained interviewers.
		F	37	Same hospitals and same time period as male patients (86% white).	37	Same as with regard to male controls. 43% had malignant and 57% benign tumors.	
Wynder and Bross 1961 (374).	India	M F	67 27	Admitted to Tata Memorial Hospital, Bombay.	134	Patients with other forms of cancer except for oral cavity and lungs; as well as various benign diseases.	(1) Interviewed by one person. (2) 10% of male cancer cases histologically confirmed and 4% of female cancer cases.

TABLE 13.—*Summary of results of retrospective studies of tobacco use and cancer of the esophagus*

Investigator, year, and reference	Percent non-smokers		Percent heavy smokers		Percent inhalers among smokers		Relative risk: ratio to non-smokers	
	Cases	Controls	Cases	Controls	Cases	Controls	All smokers	Heavy smokers
Sadowsky et al. 1953 (301)	3.8	13.2					4.0	
Sangvhi et al. 1955 (306)	5.5	17.3	Average number of bidis smoked				3.6	
			15.3	14.1				
Wynder et al. 1957 (385):								
M	13	24					2.1	
F	about 85	about 92					2.0	
Staszewski 1960 (326, 327)	0	18	95.8	59	87.5	80		16
Schwartz et al. 1961 (315)	3	17	Total amount smoked daily (cigarettes)		39	38	6.6	
			16.8	16.0				
Wynder and Bross 1961 (374):								
(1) American males	5	15	48	33			3.4	1.8
(2) American females	41	78	27	16			4.1	1.9
(3) Indian males	13	28					2.0	
(4) Indian females	78	94					4.5	

this independent variable. Since a relationship between alcohol consumption and tobacco use is known to exist, these investigators analyzed the relationship between tobacco consumption and esophageal cancer after adjusting for alcohol intake. Of extreme interest is their observation that in the absence of alcohol consumption there was no association with tobacco consumption, but in the presence of alcohol consumption an increasing relative risk with increasing number of cigarettes smoked was apparent. In the presence of alcohol consumption, a high association between esophageal cancer and cigar and pipe smoking was also noted.

PROSPECTIVE STUDIES

In the seven prospective studies (Table 1 of this Chapter) some deaths from esophageal cancer have been accumulated to date. The mortality ratios range from 0.7 in the California Occupational study to 6.6 in the Dorn study. Combining the observed deaths from this cause for all seven studies yields a total mortality ratio of 3.4. The stability of the ratios for three of the studies (84, 96, 97) is of low order, for they are based on only 7, 4 and 9 cases respectively. The mean mortality ratio for cancer of the esophagus in cigar and pipe smokers is 3.2, second only to that for cancer of the oral cavity, 3.4 (Table 24, Chapter 8). This ratio is based on 33 cases of esophageal cancer in cigar and pipe smokers in five studies.

Recently calculated data from six prospective studies (Table 23, Chapter 8) reveal a gradient of risk ratios from 3.0 for smokers of one pack or less of cigarettes per day to 4.9 for smokers of more than a pack per day. It is obvious that with so few cases to date, further cross-classification by duration of smoking, inhalation practices, and discontinued smoking is not feasible at the present time.

Carcinogenesis

So far as known, no attempts to induce carcinoma of the esophagus by tobacco smoke or smoke condensates have been reported.

A further note, indicative of needed research, is in order. In the recent Wynder and Bross study (374) these authors report that injection of ethyl alcohol into or painting of ethyl alcohol on the skin of mice promotes the carcinogenic activity of cigarette smoke condensate when applied to the skin. No data are presented in evidence.

Evaluation of Evidence

Five of the seven retrospective and six of the seven prospective studies show significant associations between esophageal cancer and tobacco consumption. One prospective study showed a mortality ratio less than unity (96) but this is based on only four observed cases among smokers. Although two of the seven retrospective studies investigating esophageal cancer did not find the smoker-excess among cases statistically significant, all showed such excesses. Furthermore, it is noteworthy that despite the variations in the quality of the control groups the calculated relative risks in the retrospective studies fall within the same range of mortality ratios as in the prospective studies. This level of consistency is not to be ignored although few of the studies revealed increasing gradients of risk with amount smoked.

Here, only two studies (301, 374) and possibly a third retrospective study (385) show such a gradient. Whether this subclass inconsistency is due to inadequacy of data because of small sample size cannot be determined at the present time.

The prospective studies have, however, revealed such a gradient for amount of cigarette smoking when the data of six studies were combined. Although not as marked a gradient as in the lung cancer group, the increase in risk for esophageal cancer among smokers of more than a pack a day is greater than for laryngeal and oral cancer.

Inhalation data are extremely sparse but in the two studies in which the data were analyzed (315, 325), no correlation could be found. This is compatible with an hypothesis that postulates an action on esophageal mucosa by swallowing of tobacco condensates or tars. Evidence for this is lacking, but the associations between esophageal cancer and several forms of tobacco use, viz., cigarette, cigar and pipe smoking and tobacco chewing, would support such an hypothesis. It is also supported by the fact that the mortality ratio for cigar and pipe smokers, though based on a relatively small number of cases, is approximately equal to the ratio for cigarette smokers (3.3 vs. 3.0).

Mortality from esophageal cancer in the United States has shown a tendency to rise slightly among whites in the last 30 years; non-whites show a greater rise, but this is usually attributed to improvement and increased availability of diagnostic facilities. The smallness of the rise does not negate the significance of an association with tobacco use, some forms of which have been concurrently rising. This has been discussed earlier but it should he emphasized that declines in other environmental factors may counterbalance the otherwise rising influence of the variable under study. Since neither prospective nor retrospective studies were executed in the decades of 1910-1930, conjectures on such an hypothesis are speculative. Inasmuch as the interaction between alcohol and tobacco use is documented in only one study, it would at the present time be unwise to attempt any more detailed evaluation of the relationship of tobacco use to trends in the incidence and mortality of esophageal cancer. Suffice it to say that, if the component of tobacco use involves the swallowing of tobacco juice, then the time trends in types of tobacco use over the past 50 years are relevant and not incompatible with the hypothesis.

Conclusion

The evidence on the tobacco-esophageal cancer relationship supports the belief that an association exists, However, the data are not adequate to decide whether the relationship is causal.

URINARY BLADDER CANCER

Epidemiologic Evidence

RETROSPECTIVE STUDIES

The experimental work of Holsti and Ermala (177) in 1955 prompted the first retrospective study of the relationship between smoking of tobacco

and cancer of the urinary bladder. After the lips and oral mucosa of albino mice of a "mixed known strain" were painted with tobacco tar daily for five months, 10 percent of the animals developed malignant papillary carcinomas of the urinary bladder. No carcinomatous change was observed in the oral cavity. The report of this work led Lilienfeld (215) to undertake a study of bladder cancer cases admitted between 1945 and 1955 at Roswe11 Park Memorial Institute. Before being seen by clinicians for diagnosis, all patients at this institution are interviewed regarding smoking histories. Lilienfeld found a significant association between cigarette smoking and urinary bladder cancer among males but not among females. This study, though carefully controlled, was done before much knowledge of cigarette smoking relationships to other diseases had accumulated and before the results of the earliest prospective study had revealed a relationship of smoking to urinary bladder cancer. Thus, information on amount smoked, age at onset of smoking, duration of smoking, and inhalation was either not collected or not analyzed.

Only three additional retrospective studies (220, 315, 389) have appeared since Lilienfeld's publication in 1956. The methodology and results of these studies are presented in Tables 14 and 15.

All of these investigators found a significant association between cigarette smoking and urinary bladder cancer in males. Three of these studies (215, 220, 389) concerned themselves with the study of female cases as well. Two of them found no relationship between smoking and urinary bladder cancer in females, but one study (389) found the relationship to be significant.

Three of the studies examined other forms of smoking. Schwartz et al. (315), in France where cigar smoking is negligible, separated pipe smokers and mixed smokers from cigarette smokers and found only a suggestion of an association with pipe smoking, but the number of cases in this category were too few for meaningful inferences. Lockwood (220) found significant associations between both pipe and cigar smoking and urinary bladder cancer in the male. Wynder and co-workers (389) found no excess frequencies of pipe-only and cigar-only smokers among the urinary bladder cases. Here, too, the number of such smokers was even smaller than in the Danish study by Lockwood.

Only two studies (220, 389) are concerned with *amount of smoking.* In each, a significant excess of heavy smokers was noted among male patients with urinary bladder cancer. In the Danish study, female cases and controls had equal proportions of heavy smokers but Wynder found only a suggestion of an excess of heavy smokers among the cases (Table 15).

Inhalation was examined in two studies, the French and the Danish (220, 315). Schwartz et al. (315) found a profound effect of inhalation on the association between smoking and urinary bladder cancer. When comparisons between cases and controls were made in each of the classes of amount smoked, the bladder cancer cases showed a greater frequency of inhalers in each class. When inhalation was controlled, the effect of amount of cigarette smoking disappeared. Thus the implication is clear that the essential relationship is between inhalation of either cigarette or pipe smoke with urinary bladder cancer. Lockwood (220) found statistically signifi-

TABLE 14.—*Summary of methods used in retrospective studies of smoking and cancer of the bladder*

Investigator, year, and reference	Country	Sex	Cases		Controls		Collection of data
			Number	Method of selection	Number	Method of selection	
Lilienfeld et al., 1956 (215).	U.S.A.	M	321	Admissions to Roswell Park Memorial Institute. 1945–55 over 45 yrs. of age.	337 287	No-disease patients. Prostate cancer.	Interview of patients by groups of interviewers at time of 1st visit to Institute before seen and diagnosed by physicians.
		F	116	Same as males	109 317 763	Benign bladder conditions. No-disease patients. Breast cancer	
Schwartz et al., 1961 (315).	France	M	214	Admissions to hospitals in Paris and a few large provincial cities since 1954.	214	Healthy individuals admitted to same hospital because of work or traffic accident-matched by 5 yr. age group, & admitted during same time to same hospital as cases.	Interviewed by team of specialized interviewers who interviewed the largest proportion possible of all cancer patients admitted to these hospitals. Cases and matched controls interviewed by same person.
Lockwood 1961 (220).	Denmark	M F	282 87	All bladder tumors reported to Danish Cancer Register during 1942–1956 and living at time of interview in Copenhagen and Fredericksburg.	282 87	A. From election rolls matched with cases according to sex, age, marital status, occupation and residence.	Cases—59 cases interviewed by Clemmesen and 310 by Lockwood. Election Roll Controls—2 interviewed by Clemmesen and 367 by Lockwood.
						B. Another control group obtained from sample of Danish Morbidity Survey (1952–53 & 54) compared with respect to smoking histories.	
Wynder 1963 (389). (To be published).	U.S.A.	M F	*First Phase* 200 50	Admission to several hospitals in N.Y.C. during January, 1957–December, 1960.	200 50	Admission to same hospitals (excluded cancer of respiratory system, upper alimentary, tract, myocardial infarction). Matched by sex and age.	Trained interviewers.
		M F	*Second Phase* 100 20	Admission to same hospital during 1961.	100 20	Same as above.	

TABLE 15.—*Summary of results of retrospective studies of smoking (irrespective of type) and cancer of the bladder*

Investigator, year, and reference	Sex	Percent non-smokers		Percent heavy smokers		Percent inhalers among smokers		Relative risk: ratio to non-smokers	
		Cases	Controls	Cases	Controls	Cases	Controls	All smokers	Heavy smokers
Lilienfeld et al., 1956 (215)	M	15	29					2.3	
	F	87	83					1.4	
Schwartz, 1961 (315)	M	11	20			54	37	2.0	
Lockwood, 1961 (220)	M	9	17	30	15	33	9	2.1	2.4
	F	56	66	4	4			1.5	1.0
Cancer Cases	M	11				24			
	F	59				14			
Papilloma Cases	M	8				31			
	F	55				14			
Wynder et al., 1963 (389) (Phase A and B combined)	M	7	18	47	23			2.9	3.0
	F	61	86	6	0			3.9	

cant relationships with inhalation also but, unfortunately, he did not attempt cross-classification of inhalation with amount and type of tobacco smoked. Schwartz analyzed this even though his numbers were smaller and his sample more heterogenous in tobacco habits than Lockwood's.

Only one study analyzed data on *age at onset of smoking*. Lockwood (220) found that his patients began smoking larger amounts of tobacco at an earlier age than did his controls.

Other variables were examined in three studies, not only as a check on possible biases and influence of confounding variables on the association (220, 315) but also as a means of eliciting other environmental factors (389). In the latter study by Wynder, which included analysis of occupation, an excess of leather workers and shoe repairers was noted among the urinary bladder cancer cases although their numbers were small. It is possible that exposure to aniline dyes also occurred.

Relative risk ratios were calculated from the data contained in the original papers, and are presented in Table 15 and 15A. For male smokers these ratios varied from 2.0 to 2.9. In one study of males (220) heavy smoking tended to increase the risk slightly (2.1 to 2.4). The female ratios were near unity except for the finding of 3.9 from Wynder's data. Relative risk ratios for male cigarette smokers only ranged from 2.0 to 3.3.

PROSPECTIVE STUDIES

Six of the seven prospective studies showed bladder cancer mortality ratios ranging from 1.7 in the current study by Best et al., in Canada (25) to 6.0 in the California occupational study of Dunn et al. (96). The only disparate finding is in the Doll and Hill study (84) where, on the basis of 12 bladder cancer deaths among the physicians of the study, the mortality ratio is 0.9 (Table 1). Two studies (96, 97) show relatively few deaths from urinary bladder cancer to date. If these studies are tentatively omitted and the remaining four studies (25, 88, 157, 163) with significantly larger numbers of deaths are scrutinized, the range of the mortality ratios is narrow: 1.7 to 2.2.

The mean mortality ratio for all seven prospective studies is 1.9. For smokers of cigars and pipes the mean mortality ratio is 0.9 (Table 22, Chapter 8). Further information on sub-classes of tobacco use, e.g., inhalation practices, age at onset of smoking, and duration of smoking are

TABLE 15A.—*Summary of results of retrospective studies of cigarette smoking and cancer of the bladder in males*

Investigator and Classification of Cigarette Smoking	Percent Cigarette Smokers		Relative Risk: Ratio of Cigarette Smokers to Non-Smokers
	Cases	Controls	
Lilienfeld (cigarette & other) (215) 1956	61	44	2.0
Schwartz (cigarette only) (315) 1961	83	70	2.1
Lockwood (Cigarette is main mode of smoking) (220) 1961	30	15	2.4
Wynder (cigarette & other) (389) 1963	85	63	3.3

not presently available. Some information on a gradient for amount of cigarette smoking was obtained from previously published data of Dorn (88) ; the mortality ratios by quantity of cigarettes were as follows: less than 10 cigarettes, 1.0; 10 to 20, 1.8; more than 20, 2.75. In the original Hammond and Horn study (163), a gradient with number of cigarettes smoked was perceptible for all cancers of the genito-urinary tract (less than 10 cigarettes, 2.0; 10-20, 2.0; more than 20, 3.4). Data for cancer of the bladder per se were not then available. In the Dorn study, even at the 1959 mark in its progress, a distinct gradient was noted. These data have recently been augmented by calculations of up-to-date data from six of the prospective studies. These reveal a distinct gradient by amount of cigarettes smoked daily. The mean mortality ratio for urinary bladder cancer among male smokers of one pack or less per day is 1.4, whereas the ratio for smokers of more than a pack is 3.1 (Chapter 8, Table 23).

Carcinogenesis

In a study whose original aim was to determine the effect of tobacco tars on the tissues of the oral cavity in mice, Holsti and Ermala (177) observed papillary carcinomas of the urinary bladder in 15 percent of the animals that survived, representing 10 percent of the 60 originally treated. The lesions were histologically classified as carcinomas, though no metastases were observed. Benign papillomatoses were observed in 87.5 percent of the animals. In a similar study, DiPaolo and Moore (75) observed only slight hyperplasia of the mucosa, but in one mouse anaplastic sarcoma of the urinary bladder was encountered. The significance of these experiments as well as earlier ones reported by Roffo (295) is obscure.

Evaluation of the Evidence

Relatively few retrospective studies of the smoking-urinary bladder cancer relationship have been undertaken. The four existing studies showed a *consistency* in association between cigarette smoking and cancer of the urinary bladder in males. Two investigators who studied. the dose-effect found a correlation of increasing risk with amount smoked. Those examining the practice of inhalation of smoke have found an even greater association and, although but one study dealt with age at onset of smoking, this showed that patients with bladder cancer started heavy smoking at an earlier age than the controls.

The relative risks calculated from data available in the retrospective studies are of an almost ‘similar order of magnitude not only among themselves but in comparison to the mortality ratios derived from the larger of the prospective studies. Two of three retrospective studies show no association with other forms of smoking and this is consistent with the findings of a bladder cancer mortality ratio of somewhat less than unity among cigar and pipe smokers as elicited from the prospective studies.

Because of this consistency in the male studies, only a brief discussion of the elements of observer-bias, misclassification, non-response bias, and other possible causes of error, will be necessary. Suffice it to say that in the

Lilienfeld study all interviewing for smoking history was done on all admissions for any complaint prior to diagnosis. In the Schwartz study, matched healthy controls were utilized, comparisons were made for area of residence, family status, and occupation: and these variables were tested for relationship to smoking and inhalation histories. Such relationships, when found, were slight and not to the degree of association of smoking to urinary bladder cancer. Information on histological confirmation of all cases of this study by Schwartz was lacking. Since the bladder cancer cases in this study had originally served as controls in a lung cancer study, some of the observer-bias arising from knowledge of the distinction between cases and controls was probably neutralized. Furthermore, the results of the early phase of the study were consistent with the findings in the entire study reported on later.

The Lockwood study, executed to elicit environmental factors which might be operating to explain an increase in Copenhagen in incidence of bladder tumors both benign and malignant, included all bladder tumors, 24 percent of which were malignant. Since differences of opinion with respect to criteria of malignancy in these tumors exists, it is possible that this type of tumor was similar to those diagnosed as cancers in other countries. Nevertheless, Lockwood's group did analyze the material separately and found the smoking relationship to both benign and malignant tumors to he essentially the same. These authors also utilized a second control group derived from the Danish Morbidity Survey. Their study control group and the probability sample from the survey were similar with respect to amount of smoking. Both cases and controls were similar with respect to alcohol consumption, marital status, housing, history of pyelitis and cystitis, sulfonamide consumption, and other variables.

The Wynder study (389) involved controls matched by age and sex and hospital of admission. Variables of comparison included race, marital status, religion, place of birth, dietary habits, education, residence, alcohol consumption, weight, oral hygiene, blood group, circumcision status, occupation, and genito-urinary diseases. Cases and controls were similar for all variables except for occupation and genito-urinary diseases. The excess of leather workers and shoe repairers among the bladder cancer cases has been noted above. The bladder cancer cases also had a higher frequency of bladder stones or cystitis. These conditions may have etiologic implications.

Several conflicting findings do exist, however, in relation to the association between smoking and urinary bladder cancer. The first is the finding by Wynder of a highly significant association between smoking and bladder cancer in females. This latter association is weakened, however, by the equivocal finding of only a slight excess of heavy smokers among the cases. A second inconsistent finding is an association with cigar smoking, as reported for males by Lockwood. Inhalation was tested by him but it is not clear whether the cigar smokers inhaled in sufficient amount and depth to characterize them as being different from cigar smokers in the United States. Finally, the urinary bladder cancer mortality ratio in the Doll and Hill prospective study is approximately unity, a finding inconsistent with the other six prospective studies. In addition to the finding of an association with smoking in female cases in a single study (389) is the fact that no association exists for women in two other retrospective studies. If cigarette smoking is ac-

tually associated with male bladder cancer, should not an association be found in the female, as with lung, larynx, oral, and possibly esophageal cancer?

The clues to the solution of this dilemma may be first, that inhalation seems to be the more important factor in the relationship between smoking and bladder cancer, and secondly, that other etiologic factors may have a "swamping" effect in the female to counteract her lower frequency of inhaling. Evidence for support of this hypothesis is lacking at present. If correct, then the Wynder finding requires explanation, which may be looked for in the disparities in smoking habits between cases and controls.

The *strength* and *specificity* of the association are obviously of low order because the mean mortality ratio is 1.9. This also implies that factors other than smoking may be associated etiologically with urinary bladder cancer.

Little can be said regarding the *coherence* of the association beyond the scanty data on dose-effect. Furthermore. adequate information is lacking for an intelligent discussion of the sex differential, which is the lowest for any of the cancer sites for which an association, direct or indirect, with smoking has hitherto been suspected.

An urban-rural differential is virtually non-existent in urinary bladder cancer. Since there seem to be differences in patterns of smoking between rural and urban groups, additional factors must he sought to account for the lack of such a differential in the disease.

The experimental work of Holsti and Ermala (177) has been described earlier. This is a solitary finding requiring repetition with the same strain of mice. DiPaolo and Moore utilizing different methods of preparation of the tobacco tar and different strains of mice obtained essentially negative results (75).

Further retrospective studies of female cases, studies with large enough numbers of male cases to provide for further cross-classification by amount and duration of smoking and inhalation practices, and the ultimately forthcoming results on female subjects in the current Hammond prospective study will be necessary to provide more nearly adequate data in urinary bladder cancer.

Conclusion

Available data suggest an association between cigarette smoking and urinary bladder cancer in the male but are not sufficient to support a judgment on the causal significance of this association.

STOMACH CANCER

Epidemiologic Evidence

RETROSPECTIVE STUDIES

Very little interest in the relationship between smoking and gastric cancer seems to exist since only four (94, 193, 315, 325) retrospective studies have appeared in the literature since 1946. The methodology and findings of these studies have been summarized in Tables 16 and 17. Of the four studies, two (94, 315) failed to find any association between smoking and gastric

TABLE 16.—*Summary of methods used in retrospective studies of smoking and cancer of the stomach*

Investigator, year, and reference	Country	Sex	Cases		Controls		Collection of data
			No.	Method of selection	No.	Method of selection	
Dunham & Brunschwig 1946 (94).	U.S.A.	M&F	40	Not clear. Patients in Dept. of Surgery, Univ. of Chicago.	40	Not clear. Patients without gastric tumor.	Not specified
Kraus et al., 1957 (193).	U.S.A.	M	56	Admissions to Roswell Park Memorial Inst., 11/48–9/51, 25–74 years of age.	677	Patients admitted to Roswell Park during same time period in following 4 diagnostic groups: (1) Digestive cancer other than esophagus or stomach. (2) Cancer—other than digestive—respiratory, urinary, skin, hemat. (3) Non-tumor diag. of digestive system other than esophagus or stomach. (4) Non-tumor diag. other than digestive—respiratory, urinary, skin, hemat. Each control group matched to cancer group by age and population size of place of residence.	Questioned by trained interviewers
Staszewski 1960 (327).	Poland	M	136	Patients admitted to Oncological Institute during 1957–59.	912	See TABLE 11	See TABLE 11. Two-thirds of cancer of stomach diagnoses were histologically confirmed.
Schwartz et al., 1961 (315).	France	M	263	See TABLE 11	263	Patients hospitalized from 1954–1956 with gastric cancer in Paris and other large cities.	See TABLE 11

TABLE 17.—*Summary of results of retrospective studies of smoking and cancer of the stomach*

Investigator, reference, and year	Percent non-smokers		Percent heavy smokers		Percent inhalers among smokers		Relative risk: ratio to non-smokers	
	Cases	Controls	Cases	Controls	Cases	Controls	All Smokers	Heavy Smokers
Dunham and Brunschwig 1946 (94)	47.5	47.5					0	
Kraus et al. 1957 (193)	19.2	24.2					1.3	
Staszewski 1960 (325)	12.5	18	75.6	59	88.2	80	1.5	2.1
Schwartz et al. 1961 (315)	16	17	Total cigarettes smoked daily		37	34	1.0	
			14.6	15.3				

cancer. The other two studies, to date, suggested an association but these were not statistically significant (193, 325). Two of the studies did not approach the smoking variable specifically but as part of attempts to examine several possible etiological factors (94, 193); the other two were specifically directed to the role of smoking (315, 325). The relative risks as calculated are not significantly different from unity.

PROSPECTIVE STUDIES

The seven prospective studies brought up-to-date (except for the original Hammond and Horn study) have yielded a total of 413 deaths from gastric cancer. The mean gastric cancer mortality ratio for the seven studies is calculated to be 1.4. This is obviously lower than for any of the sites described earlier. The individual studies, however, with fairly adequate numbers for stability, show a range of mortality ratios from 0.8 in the Dunn, Linden, Breslow occupational study (96) to 2.3 in the Hammond and Horn study (163) (Table 1 of this chapter), The Hammond and Horn ratio is not statistically significant (p=0.12) (163).

Two of the earlier reports (84, 88) provide information on mortality rates or mortality ratios for the several cigarette smoking classes by amount smoked. In neither of these is any gradient apparent.

For cigar and pipe smokers the combined studies provide a mean gastric cancer mortality ratio of 1.1 (Table 24, Chapter 8).

Carcinogenesis

Squamous cell carcinoma has been produced in the forestomach of mice by the oral administration of various polycyclic aromatic hydrocarbons (8, 19, 59, 113a, 223, 276, 308, 334, 364, 368) including benzo(a)pyrene (19, 59, 276, 364). It should be noted that the forestomach of mice and rats is covered with squamous epithelium extending down from the esophagus. The incidence of such cancers in mice varies with the strain used. Stewart and Lorenz (333) produced the same type of cancer in the forestomach by injecting 20-methylcholanthrene intramurally.

Rats also develop squamous cell tumors in the forestomach after prolonged oral administration of carcinogens (249).

Adenocarcinoma has been produced in the glandular stomach of mice and rats by the intramural injection of carcinogenic hydrocarbons (17, 19, 187, 339) or by inserting a silk thread impregnated with 2-methylcholanthrene into the glandular stomach wall between the serosa and mucosa (332, 333).

Attempts at production of cancer of the stomach with tobacco tars or condensates have not been successful (294).

Evaluation of the Evidence

Squamous and adeno-carcinomas have been produced experimentally in mice with benzo(a)pyrene and dibenz(a,h)anthracene injected directly into the fore- or glandular stomach. None of the retrospective studies shows an association between gastric cancer and smoking. Nor do the prospective studies yield gastric cancer mortality ratios significantly higher than the total

mortality ratio. In fact, the mean gastric cancer mortality ratio for cigarette smokers is below the mean total mortality ratio, and for cigar and pipe smokers it is approximately the same. Even a gradient by amount smoked is lacking in at least two of the prospective studies.

Conclusion

No relationship has been established between tobacco use and stomach cancer.

SUMMARIES AND CONCLUSIONS

Cancer deaths per year increased seven-fold (in the United States death registration area of 1900) between 1900 and 1960--from 10,000 in 1900 to 80,000 in 1960. Less than half of this increase was due to aging and growth of the population. A large part of the increase was due to lung cancer.

LUNG CANCER

While part of the rising trend for lung cancer is attributable to improvements in diagnosis, the continuing experience of the State registers and the autopsy series of large general hospitals leave little doubt that a true increase in the lung cancer death rate has taken place. About 5,700 women and 33,200 men died of lung cancer in the United States in 1961; as recently as 1955, the corresponding totals were 4,100 women and 22,700 men. This extraordinary rise has not been recorded for cancer of any other site.

When any separate cohort (a group of persons born during the same ten-year period) is scrutinized over successive decades, its lung cancer mortality rates vary directly with the recency of the birth of the group: the more recent the cohort, the higher the risk of lung cancer throughout life. Within each cohort, lung cancer mortality apparently increases unabated to the end of the life span. The pattern would suggest that the mortality differences may be due to differences in exposure to one or more factors or to a progressive change in population composition among the several cohorts.

A considerable amount of experimental work in many species of animals has demonstrated that certain polycyclic aromatic hydrocarbons identified in cigarette smoke can produce cancer. Other substances in tobacco and smoke, though not carcinogenic themselves, promote cancer production or lower the threshold to a known carcinogen. The amount of known carcinogens in cigarette smoke appears to be too small to account for their carcinogenic activity.

There is abundant evidence, however, that cancer of the skin can be induced in man by industrial exposure to soots, coal tar, pitch and mineral oils; all of these contain various polycyclic aromatic hydrocarbons known to be carcinogenic in many species of animals. Some of these compounds are also present in tobacco smoke. Although it is noted that the few attempts to produce bronchogenic carcinoma directly with tobacco extracts, smoke, or

condensates applied to the lung or the tracheobronchial tree of experimental animals have not been successful, the administration of polycyclic aromatic hydrocarbons, certain metals, radioactive substances, and certain viruses have been shown to produce such cancers. The characteristics of the tumors produced are similar to those observed in man. Since the response of most human tissues to carcinogenic substances is qualitatively similar to that observed in experimental animals, it is highly probable that the tissues of man are susceptible to the carcinogenic action of some of the same polycyclic aromatic hydrocarbons that produce cancer in experimental animals. Neither the available epidemiological nor the experimental data is adequate to fix a safe dose of chemical carcinogens for men.

The systematic evidence for the association between smoking and lung cancer comes primarily from 29 retrospective studies of groups of persons with lung cancer and appropriate "controls" without lung cancer and from 7 prospective studies (described in Chapter 8). The 29 retrospective studies of the association between tobacco smoking and lung cancer (summarized in Tables 2 and 3 of Chapter 9) varied considerably in design and method. Despite these variations, every one of the retrospective studies showed an association between smoking and lung cancer. All showed that proportionately more heavy smokers are found among the lung cancer patients than in the control populations and proportionately fewer non-smokers among the cases than among the controls.

The differences are statistically significant in all the studies. Thirteen of the studies, combining all forms of tobacco consumption, found a significant association between smoking of any type and lung cancer; 16 studies yielded an even stronger association with cigarettes alone. The degree of association between smoking and lung cancer increased as the amounts of smoking increased. Ex-smokers generally showed a lower risk than current smokers but greater than non-smokers. Relatively few of the retrospective studies have dealt with "age started smoking," but all except one of these studies found that male lung cancer patients began to smoke at a significantly younger age than the controls. Except at the highest cigarette consumption levels, the relationship of inhalation to lung cancer was significant for those smoking cigarettes alone.

Several investigators have utilized mathematical techniques to calculate, from retrospective studies, the relative risks of lung cancer for smokers as compared with non-smokers. All of the 9 studies in which relative risk ratios were derived showed a significantly greater risk among smokers, ranging from as low as 2.4-to-1 for light smokers to as much as 34.1-to-1 for heavy smokers, with most of the ratios between these two extremes.

All seven of the prospective studies show a remarkable consistency in the higher mortality of smokers, particularly from lung cancer. Of special interest is that the size of the association between cigarette smoking and total lung cancer death rates has increased with the ongoing progress of the studies. Depending on the kind of population studied, the relative risks of lung cancer for current cigarette smokers in America compared with non-smokers range from 4.9 in one study to 15.9 in another. A study among British doctors showed a ratio of 20.2. For the studies as a whole, cigarette smokers have a risk of developing lung cancer 10.8 times greater than non-

smokers. The mortality ratios increase progressively with amount of smoking: the pivot level appears to be 20 cigarettes a day. For those who smoke pipes and/or cigars (to the exclusion of cigarettes), the lung cancer ratios are lower than for any of the cigarette smoking classes including combinations of cigarettes with pipe and / or cigars.

In extensive and controlled blind studies of the tracheobronchial tree of 402 male patients, it was observed that several kinds of changes of the epithelium were much more common in the trachea and bronchi of cigarette smokers and subjects with lung cancer than in non-smokers and patients without lung cancer. The epithelial changes observed are (1) loss of ciliated cells, (2) basal cell hyperplasia (more than two layers of basal cells), and (3) presence of atypical cells. Each of the three kinds of epithelial changes was found to increase with the number of cigarettes smoked. Extensive atypical changes were seen most frequently in men who smoked two or more packs of cigarettes a day. Men who smoke pipes or cigarettes have more epithelial changes than non-smokers but have fewer changes than cigarette smokers consuming approximately the same amount of tobacco. It may be concluded, on the basis of human and experimental evidence, that some of the advanced epithelial lesions with many atypical cells, as seen in the bronchi of cigarette smokers, are probably pre-malignant.

Other pathologic studies show that squamous and oval-cell carcinomas are the predominant types associated with the increase of lung cancer in the male population, and that a significant relationship exists between smoking and the epidermoid and anaplastic types. In several studies, adenocarcinomas have also shown a definite increase, although to a lesser extent. Various studies have suggested that adenocarcinomas have little or less relationship to smoking.

In general, the association between smoking and lung cancer may be measured by certain crude indirect indicators as well as by the direct measures (retrospective and prospective studies) described earlier. Indirect measures include: a parallel increase in lung cancer mortality rates and in per capita consumption of tobacco: disparities between male and female lung cancer rates and the corresponding differences between smoking habits of men and women by amounts smoked and duration of smoking.

The retrospective and prospective studies directly measure the occurrence and relationship of smoking and lung cancer in the same kinds of population. Careful analysis of thee studies demonstrates that neither diagnostic errors nor classification errors in terms of amount smoked are of sufficient size to invalidate the results. Possible bias due to selection of subjects is diminished by the fact that in the continuing studies, lung cancer death rate differentials increase with the passage of time. Thus, it would appear that an association between cigarette smoking and lung cancer does indeed exist.

No single criterion is sufficient to evaluate the causal significance of this association, but a number of different kinds of criteria, considered together, provide an adequate test: the association is *consistent:* no prospective study and no reasonably designed retrospective study has found results to the contrary. In the nine retrospective studies for which relative risks for smokers and non-smokers were calculated, and in the seven prospective studies, the relative risk ratios for lung cancer were uniformly high and remarkably

close in magnitude, attesting to the *strength* of the association. Moreover a dose-effect phenomenon is apparent in that the relative risk ratio increases with the amount of tobacco consumed or of cigarettes smoked. From the prospective studies, it is estimated that in comparison with non-smokers, average smokers of cigarettes have approximately a 9- to 10-fold risk of developing lung cancer and heavy smokers at least a 20-fold risk.

An important criterion for the appraisal of causal significance of an association is its *coherence* with known facts of the natural history and biology of the disease. Careful examination of the natural history of smoking and of lung cancer shows the relationship to be coherent in every aspect that could be investigated. The probability that genetic influences might underlie both the tendency toward lung cancer and the tendency to smoke were also examined. The great rise in lung cancer recorded in man, that has occurred in recent decades, points to the introduction of new determinants without which genetic influences would have had little or no potency. The genetic factors in man were evidently not strong enough to cause the development of lung cancer in large numbers of people under environmental conditions that existed half a century ago. The assumption that the genetic constitution of man could have changed gradually, simultaneously, and identically in many countries during this century is most unlikely. Moreover, the risk of developing lung cancer diminishes when smoking is discontinued, although the genetic constitution must be assumed to have remained the same.

It has been recognized that a causal relationship between cigarette smoking and lung cancer does not exclude other factors. Approximately 10 percent of lung cancer cases occur among non-smokers. The available evidence on occupational hazards, urbanization or industrialization and air pollution, and previous illness was considered for possible etiologic factors.

A significant excess of lung cancer deaths was found among workers in certain industries-notably chromate, nickel processing, coal gas, and asbestos-but the population exposed to industrial carcinogens is relatively small; these agents cannot account for the increasing lung cancer risk in the general population. The urban-rural differences in lung cancer mortality risk, though small and accounted for in part by differences in smoking habits, imply that intensity of urbanization or industrialization and air pollution may have a residual influence on lung cancer mortality. Observations on previous respiratory illness are too few in number to place any degree of assurance on relationship with lung cancer.

Conclusions

1. Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction.

2. The risk of developing lung cancer increases with duration of smoking and the number of cigarettes smoked per day, and is diminished by discontinuing smoking.

3. The risk of developing cancer of the lung for the combined group of pipe smokers, cigar smokers, and pipe and cigar smokers is greater than in non-smokers, but much less than for cigarette smokers. The data are insufficient to warrant a conclusion for each group individually.

ORAL CANCER

The suspicion of an association between use of tobacco and oral cancer dates back to the early 18th century when cancer of the lip was first noted among users of tobacco. In modern times, 20 retrospective studies have shown a significant association of oral cancer with smoking or chewing of tobacco or use of snuff. Associations between oral cancer and smoking of cigarettes, cigars, and pipes were noted in nearly all of these studies, but in many of them pipes and cigars seemed to exert a stronger influence.

In a study in which the sample size was large and controls adequate, it was possible to establish gradients for lip cancer by number of pipefuls smoked a day, for tongue cancer by amount of tobacco in pipes and cigars, and oral cancers by number of pipefuls. No gradient by amount smoked was noted for cigarettes.

The seven prospective studies show that cigarette smokers have proportionately 4.1 times as much mortality from oral cancer as non-smokers. This is the third highest mortality ratio of cigarette smokers to non-smokers among the several specific types of cancer deaths and the fourth highest among all causes of death associated with cigarette smoking. For cigar and pipe smokers compared with non-smokers, oral cancer has the highest mortality ratio, 3.3, of all causes of death, exceeding cancer of the esophagus, larynx, and lung.

Cancer of the oral cavity has not been produced experimentally by the exposure of animals to tobacco smoke or to carcinogenic aromatic polycyclic hydrocarbons except in the special case of benzo(a)pyrene and other hydrocarbons on the cheek pouch of the hamster. Leukoplakia was reported to have been induced by the injection of tobacco smoke condensates into the gingiva of rabbits. A strong clinical impression links the occurrence of leukoplakia of the mouth with the use of tobacco in its various forms.

Conclusions

1. The causal relation of the smoking of pipes to the development of cancer of the lip appears to be established.

2. Although there are suggestions of relationships between cancer of other specific sites of the oral cavity and the several forms of tobacco use, their causal implications cannot at present be stated.

LARYNX

Retrospective studies with adequate sample size all designate cigarette smoking as the most significant class associated with cancer of the larynx.

In each of the seven prospective studies, laryngeal cancer has been observed among smokers in frequencies in excess of the expected. A summation yields a mean mortality ratio of 5.3 for cigarette smokers.

Recently calculated material from six prospective studies shows a gradient of risk ratios from 5.3 for smokers of one pack or less of cigarettes per day to 7.5 for smokers of more than a pack per day. Laryngeal cancer cases were also associated with cigar and pipe smoking, but the number of cases is not yet large enough for judgment.

The relative strength of the association, as measured by the specific mortality ratio (as an average of combined experiences), is not as high as that noted for lung cancer, but two of the three major studies with adequate case loads indicate that the real value of the relative risk may approach that for lung cancer. As with lung cancer, a dose-effect of smoking is also demonstrable. The majority of the retrospective studies have shown a greater association with heavy smoking. So far as known, no attempts to induce carcinoma of the larynx by tobacco smoke or smoke condensates have been reported.

Conclusion

Evaluation of the evidence leads to the judgment that cigarette smoking is a significant factor in the causation of laryngeal cancer in the male.

ESOPHAGUS

Both the retrospective and prospective studies show an association between esophageal cancer and tobacco consumption. In the seven prospective studies, smokers have died of esophageal cancer 3-4 times as frequently as non-smokers; the mortality ratio for pipe and cigar smokers (compared to non-smokers) is 3.2, second only to that for oral cancer. Recent data from six of the prospective studies show a gradient of risk ratios from 3.0 for smokers of one pack or less of cigarettes per day to 4.9 for smokers of more than a pack per day.

So far as known, no attempts to induce carcinoma of the esophagus by tobacco smoke or smoke condensates have been reported.

Conclusion

The evidence on the tobacco-esophageal cancer relationship supports the belief that an association exists. However, the data are not adequate to decide whether the relationship is causal.

URINARY BLADDER

In 1955, when the lips and oral mucosa of mice were painted with tobacco tars for five months, 10 percent of the animals developed carcinoma of the urinary bladder. This experimental work led to four retrospective studies, all of which found a significant association between cigarette smoking and

urinary bladder cancer in males. Two of the studies also found significant associations with pipe or cigarette smoking. Compared with non-smokers, the relative risk of smokers developing cancer of the urinary bladder varied from 2.0 to 2.9.

The mean mortality ratio--cigarette smokers to non-smokers--for all seven prospective studies is 1.9. Among smokers of one pack or less per day the mortality from urinary bladder cancer is 1.4 times that of non-smokers: for smokers of more than a daily pack, it is 3.1.

Conclusion

Available data suggest an association between cigarette smoking and urinary bladder cancer in the male but are not sufficient to support judgment on the causal significance of this association.

STOMACH

None of the retrospective studies shows an association between gastric cancer and smoking. The prospective studies show that cigarette smokers die of gastric cancer 1.4 times more often than non-smokers, but this is below the total mortality ratio. No gradient of risk by amount smoked is apparent.

Attempts to produce cancer of the stomach in experimental animals with tobacco tars have not been successful.

Conclusion

No relationship has been established between tobacco use and stomach cancer.

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