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CHAPTER 2

CANCER

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CHAPTER 2

CANCER

LUNG CANCER

Introduction

An estimated 72,000 people died of lung cancer in the United States in 1973 (*CA 28*). For males in the age groups 35 to 54 and 55 to 74, cancer is the second leading cause of death, and the lung is the most common site of cancer in these age groups. For men over 75, cancer is the third leading cause of death, and lung cancer trails only cancer of the prostate as the most common cancer in this age group. For women of all ages, lung cancer is now the fourth leading cause of death from cancer, and for both sexes combined, cancer is the second leading cause of death overall.

Cigarette smoking has been identified as the major cause of lung cancer. Epidemiologic, autopsy, and experimental data reviewed in the original Surgeon General's Report and in previous editions of The Health Consequences of Smoking (1967, 1968, 1969, 1971, 1972, 1973) strongly support this causal relationship and are summarized below:

1. A strong relationship between cigarette smoking and lung cancer mortality in men has been demonstrated in numerous prospective and retrospective studies with risks for all smokers as a group ranging from 7.61 to 14.20 times those of nonsmokers.

2. A dose-response relationship between cigarette consumption and the risk of development of lung cancer for both men and women has been demonstrated in numerous studies, with risks in men for heavy smokers ranging from 4.9 to 23.9 times those of nonsmokers.

3. Many investigators in the past have utilized Kreyberg's system of classification of the histopathologic types of lung cancer

(Group I—Epidermoid and oat cell carcinoma; Group II—Adenocarcinoma, bronchio-alveolar cell carcinoma, carcinoid tumor, and mucous gland tumor). The results from many studies in the past have shown a strong association between Group I tumors and cigarette smoking and data from some of these and other studies have revealed an association between adenocarcinoma (Group II tumors) and smoking. However, the association between adenocarcinoma and smoking is not as strong as that demonstrated for Group I tumors, and not all data consistently demonstrate such an association.

4. Although the incidence of lung cancer in women is lower than that for men and data on lung cancer in women are sparse, results from prospective and retrospective studies have demonstrated an association between cigarette smoking and lung cancer mortality in females.[1]

5. The relationships described above have been shown for Caucasian, Negro, Japanese, and Arabic populations.

6. Mortality from lung cancer directly attributable to cigarette smoking is increased in the presence of the "urban factor" and occupational hazards, including uranium mining and exposure to asbestos.

7. The combination of cigarette smoking and occupational exposures to radon daughters in uranium mining or to asbestos have been shown to produce additive and/or synergistic increases in the risk of development of lung cancer.

8. Data from prospective and retrospective studies reveal an increased risk of development of lung cancer in pipe and cigar smokers compared to nonsmokers, but the risk is less than that of cigarette smokers. The differences in mortality from lung cancer between cigarette smokers and pipe and cigar smokers are consistent for differences in inhalation patterns of these two groups of smokers.

9. Dose-response relationships for amount smoked have been demonstrated for pipe and cigar smokers.

10. Evidence has been presented which indicates that cessation of smoking results in a lowered risk of mortality from lung cancer in comparison with the risk of continuing smoking.

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[1] Differences in the incidence in lung cancer of men and women may be explained, at least in part, by differences in numbers of cigarette smokers, amount of daily consumption of tobacco, inhalation patterns, use of filter vs. nonfilter cigarettes, occupational exposure, as well as biologic differences in susceptibility to lung cancer.

11. Results from autopsy studies have shown that changes in the bronchial mucosa which are thought to precede development of frank bronchogenic carcinoma are found more commonly in smokers than in nonsmokers. Many of the studies demonstrated dose-response relationships for these changes.

12. Experimental studies have demonstrated that dogs which chronically inhale cigarette smoke may develop lung tumors. Intratracheal instillation of several fractions of cigarette smoke have resulted in the production of lung tumors in hamsters. Numerous subfractions of tobacco and tobacco smoke have been shown to have skin-tumor promoting activity in mice.

13. Cell and tissue culture studies have demonstrated that constitutents found in tobacco and cigarette smoke condensate (CSC) may produce malignant transformation of tissues, as well as nonspecific changes in cells.

14. Numerous complete carcinogens and cocarcinogens (tumor promoters) have been isolated from and identified in cigarette smoke condensate.

Most of the studies reviewed in the last year confirmed the knowledge of the relationship between cigarette smoking and cancer. A listing of these studies appears in a separate section of the Supplemental Bibliography. A number of studies extended the knowledge of the association between cigarette smoking and cancer, but several studies presented data which were either partially or wholly inconsistent with the known relationships; these two types of studies are reviewed below.

Lung Cancer in Men

Epidemiologic Studies

Tokuhata (*CA 32*) collected data on the families of 270 lung cancer patients and noted familial aggregations for both lung cancer mortality and the cigarette smoking habit. He postulated an autosomal recessive inheritance model for susceptibility to development of lung cancer. However, when the familial aggregation of lung cancer (familial host factor) was controlled for, cigarette smokers still had approximately 5.3 times greater mortality from lung cancer than nonsmokers.

Jha, et al. (*CA 11*) reviewed 25 histologically proven cases of lung cancer in India and found that only 48 percent of the

patients were regular smokers (6 heavy and 6 light smokers). A total of 36 percent of the tumors were adenocarcinoma and large cell undifferentiated carcinoma.

Histopathologic Studies

In an analysis of the 10-year follow-up data from the Philadelphia Pulmonary Neoplasm Research Project, Weiss, et al. (*CA 35*) followed 6,027 men prospectively, including 830 nonsmokers, with semiannual photofluorograms and observed the development of lung cancer in 121 men, 94 cases being proved histologically. All cases of lung cancer occurred among smokers. Analysis of the 67 cases of lung cancer occurring among the 2,580 men who were current smokers at the time of initial observation revealed dose-response relationships for number of cigarettes smoked per day ($P < .01$). Utilizing the WHO criteria for classification of histologic types of lung cancer, the authors found dose-response relationships for smoking and squamous cell carcinoma in toto ($P < .01$), well-differentiated squamous cell carcinoma ($P < .01$), small cell (oat cell) carcinoma ($P < .05$,) and adenocarcinoma ($P < .05$). No dose-response relationship was demonstrated for poorly differentiated squamous cell or large cell carcinoma. The dose-response curve for adenocarcinoma was based on only 14 cases, and for oat cell carcinoma on only 8 cases.

Yesner, et al. (*CA 42*) reviewed 449 biopsies of autopsy-proven cases of lung cancer seen at the Yale-New Haven and West Haven Veterans Administration Hospitals between 1953 and 1959. By utilizing the current WHO criteria for classification of lung cancer, the authors found a considerable number of discrepancies in interpretation and classification of the histologic material between the time of initial diagnosis and the present review of the material. A total of 90 percent of the cases of lung cancer occurred among cigarette smokers; 62.4 percent of the cigarette smokers with lung cancer had either epidermoid or oat cell carcinoma, as compared with 19 percent of the nonsmokers ($P < .001$). A strong relationship was demonstrated between smoking and the development of epidermoid and oat cell carcinomas, but dose-response relationships could not be demonstrated for epidermoid carcinoma. The authors suggested that a reappraisal of associations between specific histopathologic features of lung cancer and smoking may be warranted.

Histopathologic Studies

Kennedy (*CA 12*) reviewed 168 cases of lung cancer in women at the Sheffield Royal Infirmary diagnosed from 1955 to 1971. Smoking information was obtained from 112 charts. In each 4-year interval, there was an increased number of cases of lung cancer compared with the preceding interval, with increases in squamous cell and adenocarcinomas predominating. Unfortunately, changes in the incidence of lung cancer at the Sheffield Royal Infirmary cannot be determined, since the total number of women autopsied during the different time periods was not given. Kreyberg Group I tumors were about 4 times more frequent than Group II tumors in smokers, but only 2.2 times more frequent in nonsmokers. This difference was not statistically significant. After combining the results of this study with those of three other British studies, the author concluded that cigarette consumption ". . . has little influence on the histological appearance of lung cancer in British women." Limitations in the analysis of the data restrict the conclusions which may be drawn from this study, because of confusion in the histologic classification of the cases of lung cancer cited in this article.

Relationships Between Pipe and/or Cigar Smoking and Lung Cancer

Wynder and Mabuchi (*CA 39*) reported on a retrospective study of 30 male patients with lung cancer who smoked exclusively cigars and/or pipes. A control group of current smokers of pipes and/or cigars without smoking-related cancers was matched with the cases for age. The authors found a 2.75 times higher prevalence of Kreyberg Group I tumors than Group II tumors in the lung cancer group. The average age of the pipe or cigar smoking lung cancer patients with Group I tumors was approximately 9 years greater than cigarette smoking lung cancer Group I patients; however, the cigar and pipe smokers began smoking about one decade later than the cigarette smokers. Among pipe and cigar smokers, the lung cancer patients inhaled more frequently than the age-matched controls, but the numbers were too small to draw statistically significant conclusions. The lung cancer group contained relatively fewer individuals who smoked both cigars and pipes ($P < .025$). A dose-response relationship was demonstrated; there was a significantly greater percentage of heavy cigar smokers (greater than 4 cigars per day, $P < .005$) and heavy pipe smokers (greater than 10

pipefuls per day, P <.05) within the lung cancer group than among the controls.

Tidings and Bross (*CA 31*) studied 71 white male cigar/pipe smokers with lung cancer from the Roswell Park Memorial Institute and found no dose-response relationship for cigars, and although the authors stated that no such relationship existed for pipes either, there was a trend toward greater amounts of pipe tobacco consumed in the lung cancer group, especially for more than 10 pipefuls. In neither study did "occasional" cigar smokers appear in the lung cancer group (P <.05).

Secular Trends of Lung Cancer in Women

In an analysis of The U.S. Vital Statistics, Silverberg and Holleb (*CA 28*) projected an 18 percent increase in deaths due to lung cancer in males in 1973 and a 34 percent increase in deaths from lung cancer in 1973 for females compared with 1968 statistics.

Analysis of recent data from Alameda County, California (*CA 1*), confirms this increase in lung cancer incidence among women (figures 1 and 2).

In a review of the national and worldwide statistics on mortality from lung cancer, Schneiderman and Levin (*CA 25*) observed that the mortality rate from lung cancer in men continues to rise, although the rate of rise has diminished over the past decade (figure 3), in concordance with the downward trend in smoking being observed in men (figure 4). On the other hand, the rate of rise in the incidence of lung cancer in women continues to go up (figure 5), resulting in a narrowing of the sex ratio from a high in 1960 to 6.8:1 to a level of approximately 5.8:1 in 1967 (figure 6). The increase in the percentage of women who smoke correlates well with this rising incidence of lung cancer. The male:female mortality ratio is expected to narrow still further, mostly due to the rising incidence of lung cancer in women. The authors stated that the epidemic of lung cancer in women has not yet reached its peak, and if women continue to smoke, the incidence of lung cancer can be expected to rise still further.

Factors Involved in Reducing the Risk of Lung Cancer in Cigarette Smokers

In a series of 88 lung cancer patients, Wynder and Hoffmann (*CA 37, 38*) found that 73 percent of filter smokers and 65 percent of nonfilter smokers with lung cancer smoked more than

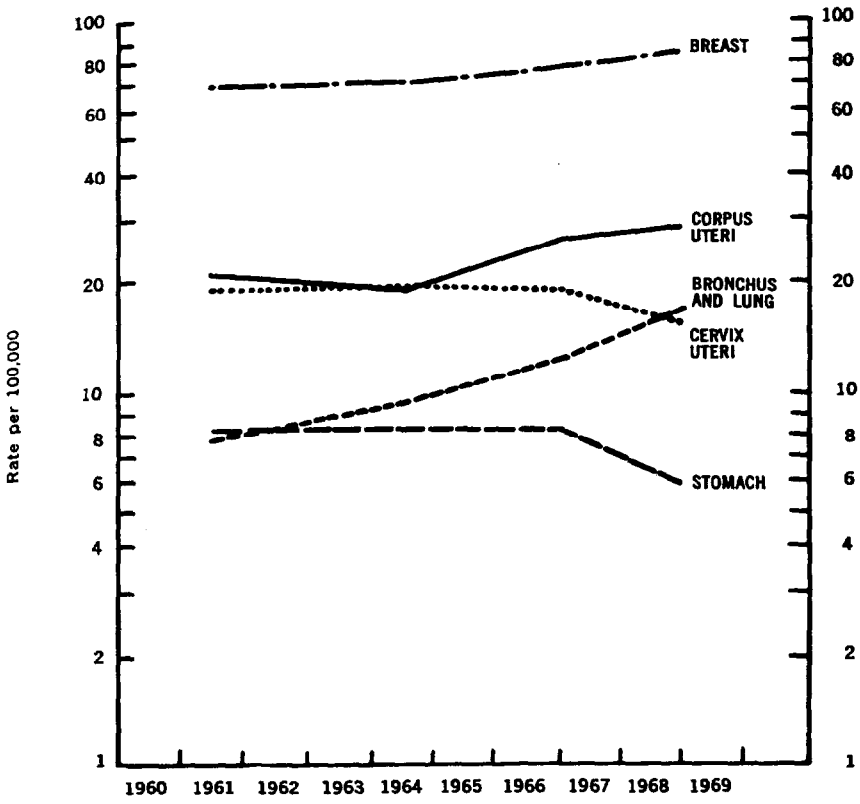

FIGURE 1.—Trends in age-adjusted cancer incidence rates for selected sites (1960–69). White females.

SOURCE: Arellano, M. G., et al. (*CA 1*).

20 cigarettes per day compared to 50 percent of lung cancer patients who smoked similar amounts in 1950. The authors attributed these findings to the reduced amount of carcinogens contained in today's nonfilter cigarettes compared with 20 years ago, and then concluded that the long-term smoker of today's nonfilter cigarettes has a lesser risk of developing lung cancer than the smokers of the nonfilter cigarettes of 1950 (all other measurements of cigarette smoking dosage being equal). Methods of selection of patients were not presented.

Occupational Risks Contributing to the Development of Lung Cancer

In a recent prospective study of 11,656 male members of the Insulation Workers Union in the United States and Canada

whose smoking habits were known (*CA 15*), a dramatic difference was found between the observed and expected incidences of lung cancer among smokers. Among 2,066 men with no history of cigarette use, 2 lung cancer deaths occurred where 5.98 deaths were expected. Among the 9,590 cigarette smokers, 134 deaths due to lung cancer were observed and only 25.09 were expected. These results confirm the synergistic effect of asbestos exposure and cigarette smoking on the risk of development of lung cancer.

In a retrospective study of mortality among 93 female asbestos workers who died between 1960 and 1970 and whose smoking habits were known, Newhouse, et al. (*CA 17*) reported that 16 women died of lung cancer. Fourteen of these women had a history of smoking (87.5 percent), whereas only 65 percent of the total number of deceased women were smokers. This difference is statistically significant ($P < .05$). In a separate publication

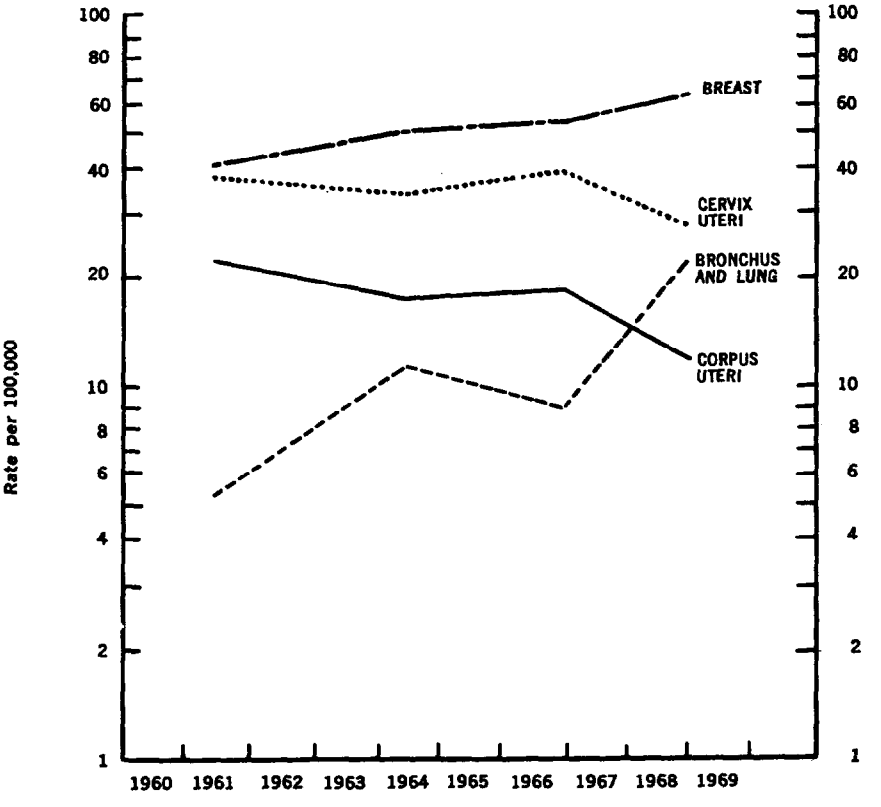

FIGURE 2.—Trends in age-adjusted cancer incidence rates for selected sites (1960–69). Negro females.

SOURCE: Arellano, M. G., et al. (*CA 1*).

(*CA 2*), these workers reported that the interaction of cigarette smoking and asbestos exposure in women, as well as in men, appeared to be multiplicative.

Experimental Studies
Experiments on Humans and Autopsy Material

Heidendal, et al. (*CA 8*) used the Xenon-133 washout technique to detect and localize a clinically and radiographically occult bronchogenic malignancy in one man by observing decreased pulmonary clearance of the radioisotope in the region of the tumor. They then used the same procedure on 10 long-term smokers with chronic coughs but no clinical signs of severe COPD

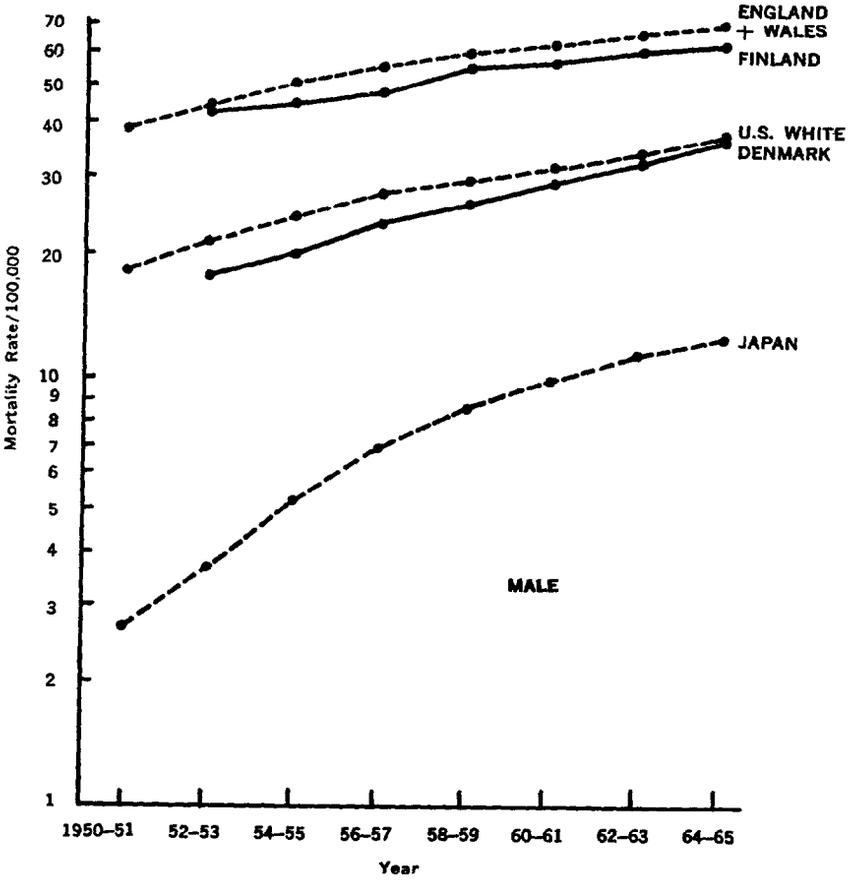

FIGURE 3.—Time trend: Age-adjusted mortality rates from lung cancer (ICD 162 and 163) for men.

SOURCE: Schneiderman, M. A., Levin, D. L. (*CA 25*).

and 10 non or ex-smokers and found no differences in their pulmonary clearance of the radionuclide. The authors felt that the Xenon washout scintiscan may be of use in high risk individuals for the detection and localization of occult lung carcinomas. This technique may be of special benefit to patients with positive or highly suspicious sputum cytologies and negative chest roentgenograms and bronchoscopies.

In an experimental study using silastic casts of the human tracheobronchial tree, Schlesinger and Lippmann (*CA 24*) were able to show that for particles of varying sizes, the mean deposition efficiency of the segmental bronchi corresponded very closely to the distribution of bronchogenic carcinoma in those segments (table 1). The limitations of this experimental model are discussed in detail by the authors.

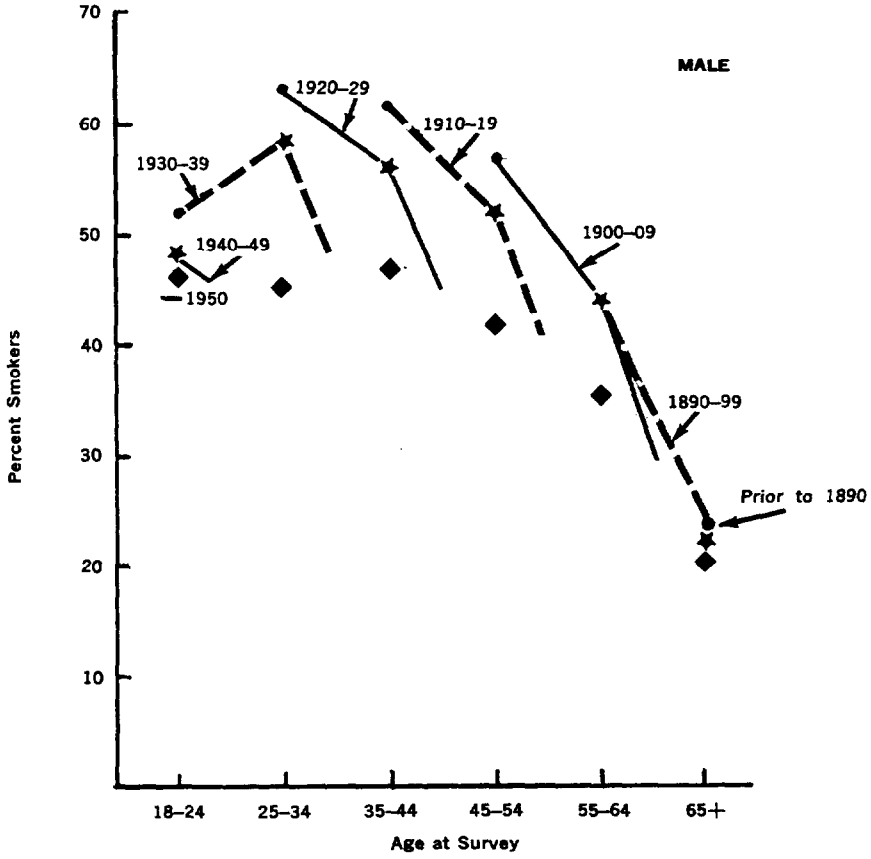

FIGURE 4.—Trends in smoking for U.S. men. Percentage of smokers reported as "currently smoking cigarettes" on surveys taken in 1955 (●), 1966 (★), and 1970 (◆), plotted by age at survey and year of birth cohorts.

SOURCE: Schneiderman, M. A., Levin, D. L. (*CA 25*).

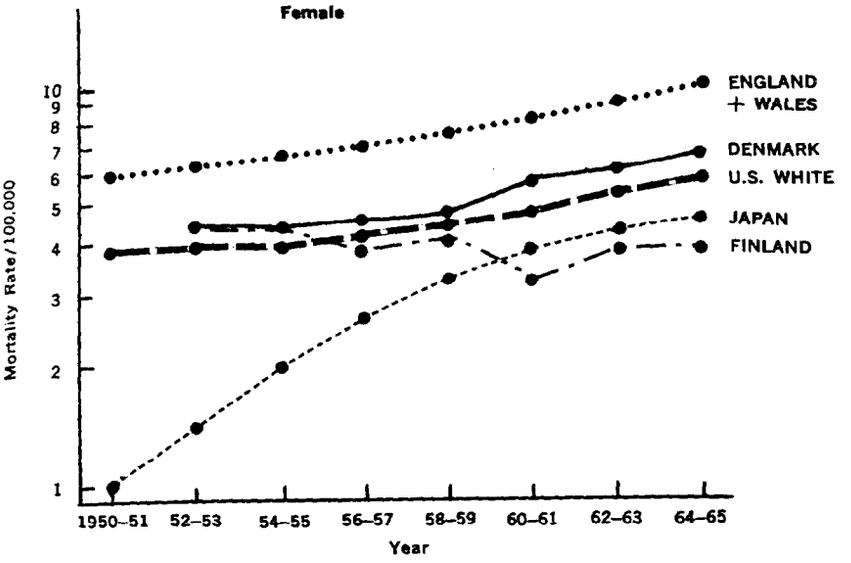

FIGURE 5.—Time trend: Age-adjusted mortality rates from lung cancer (ICD 162 and 163) for women.

SOURCE: Schneiderman, M. A., Levin, D. L. (*CA 25*).

Hoffmann (*CA 10*) has calculated that a heavy cigarette smoker (greater than 30 cigarettes per day) living in a pollutant free environment will inhale from his cigarettes approximately 800 times as much particulate matter (by weight), and approximately 20 times as much benzo(a)pyrene (by weight), as a nonsmoker living in a polluted city environment. The author stated that as much as 95 percent of the pollutant particles and benzo(a)pyrene will be retained within the lungs

TABLE 1.—*Sites of origin of bronchial carcinoma and deposition efficiency for particles in the segmental bronchi*

Lobe Bronchus	Mean Percentage of Total Carcinomas Originating in Lobar Generation which Originate in Each Branch	Mean Efficiency [a] of Each Lobe Bronchus as Percentage of Total Efficiency of Lobar Generation
Right upper	33.5	31.4
Right middle	7.5	6.2
Right lower	19.4	18.6
Left upper	26.0	29.6
Left lower	13.6	14.2

[a] Mean values for deposition efficiency were used because of the range of particle sizes of environmental contaminants which could possibly cause the production of lesions on the respiratory epithelium.

SOURCE: Schlesinger, R. B., Lippmann, M. (*CA 24*).

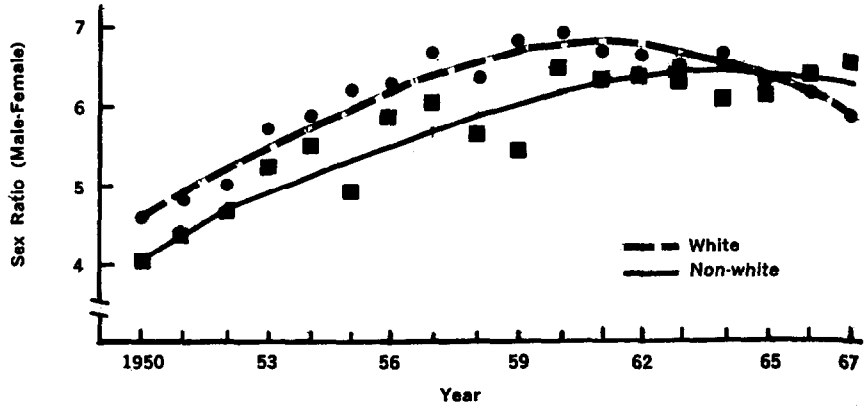

FIGURE 6.—Sex ratio of mortality rates from lung cancer (ICD 162 and 163) for United States.

SOURCE: Schneiderman, M. A., Levin, D. L. (*CA 25*).

of the smoker, while the city dweller retains a smaller fraction of the inhaled material.

Respiratory Tract Carcinogenesis in Animals

In a follow-up study of carcinogenesis of the respiratory tract induced by benzo(a)pyrene and ferric oxide in hamsters, Saffiotti, et al. (*CA 22*) found dose-response relationships for number of tumors per tumor-bearing animal when varying doses of the carcinogen were given in weekly doses intratracheally. Again, the bronchus was the most affected site, and squamous cell carcinoma the most common tumor induced. The latency period for deaths of tumor-bearing animals varied inversely with the tumor dose.

Sellakumar, et al. (*CA 27*), using the same animal model, maintained the concentration of intratracheal benzo(a)pyrene at a constant level, but increased the amount of ferric oxide carrier two and threefold and found no change in the rate of tumor production. Although ferric oxide appears to be necessary for the production of lung tumors in hamsters, particularly when small doses of benzo(a)pyrene are used (the mechanism involves increasing the duration of contact with and the degree of penetration of benzo(a)pyrene into the bronchial and pulmonary tissue), the ferric oxide does not appear to be exerting an independent carcinogenic effect, since no dose-response relationship was noted when the amount of Fe_2O_3 was varied.

In experiments in which benzo(a)pyrene was injected intratracheally into Syrian Golden hamsters weekly for 52 weeks, Feron, et al. (*CA 4*) found dose-response relationships for the

development of respiratory tract tumors, including squamous cell carcinomas of the trachea, bronchi, and bronchiole-alveolar regions. No ferric oxide carriers were employed in this set of experiments. Although squamous cell carcinomas were not the most common tumors produced, they appeared only in those animals receiving the two highest concentrations of benzo(a)-pyrene and in a dose-response relationship. When these results are compared with those from experiments in which ferric oxide was used as a carrier for benzo(a)pyrene, a lower yield of tumors and a longer latency period for the development of tumors were observed. These experiments suggest that ferric oxide need not be present for benzo(a)pyrene to produce lung tumors in the Syrian Golden hamster.

Stanton, et al. (*CA 29*) described a new animal model for the induction of epidermoid carcinomas of the lung. They injected beeswaxtricaprylin pellets intrathoracically in rats and observed that those pellets which contained cigarette smoke condensate (CSC) or the heptane soluble fraction (HSF) of CSC produced epidermoid carcinomas of the lung in 31 of 106 rats. Neither the pellets by themselves nor inclusion of unsmoked tobacco or tobacco ash within the pellets produced this carcinomatous change. The authors concluded that this animal model will be useful for detecting particular carcinogens found in cigarette smoke condensate. The authors stated that, on the basis of their findings, the pulmonary carcinogen(s) found in cigarettes "must be formed and contained in the smoke of the burning cigarette."

Mohr, et al. (*CA 14*) described experiments performed on 10 common European hamsters in which weekly subcutaneous injections of N-diethylnitrosamine resulted in tumors of the nasal cavities, larynx, trachea, and bronchi, including two squamous cell carcinomas of the lung. "Most" bronchi showed metaplastic changes. The two cases of lung cancer were found in the animals who survived to 25 weeks. The authors postulated that if longer survivals were achieved in some of the other animals, more bronchogenic tumors may have been produced.

The Role of Infection in the Development of Lung Cancer

Cigarette smokers have a higher incidence of chronic pulmonary infections than nonsmokers. Cigarette smoking has been shown to be the major cause of chronic bronchitis. However, the possible role of pulmonary infections in the development of lung cancer is less clear, since cigarette smoking is the major cause of chronic bronchitis and lung cancer. The ability of cigarette smoking to contribute to the development of pulmonary infections may also be responsible for some of the effect of

smoking on pulmonary carcinogenesis. Postulated mechanisms include enhancing the repair processes of bronchial epithelial cells, increasing the size of the transformation-susceptible population of cells, disturbing pulmonary clearance of inhaled carcinogens, inhibiting pulmonary immune mechanisms, and enhancing or inhibiting metabolism of carcinogens (*CA 16, 26*).

Nettesheim, et al. (*CA 16, 26*) conducted experiments on the possible influence of pulmonary infection in the development of lung cancer, utilizing several animal models and different infectious agents. They reported that mice exposed to influenza virus in conjunction with smog or $CaCrO_4$ had a reduced incidence of pulmonary adenomas and adenocarcinomas compared to that of mice exposed solely to the pollutants. The acute inflammatory response of the animal to this particular virus may have been responsible for the decreased incidence of tumors in these animals. In a study of rats with chronic murine pneumonia (CMP) (*CA 26*), addition of N-nitrosoheptamethyleneimine (a cyclic nitrosamine) to the rats' drinking water resulted in an increased incidence of squamous cell carcinomas of the lung in male rats, as well as a higher number of tumors per animal in those with CMP compared with uninfected male rats ($P < .005$). For female rats, the dose of carcinogen administered was very high, which may have unintentionally obscured possible differences between infected and uninfected rats. In studies designed to assess pulmonary clearance, these authors found that animals exposed to influenza virus had impaired lower respiratory tract pulmonary clearance. This impairment of clearance was observed acutely and chronically, and may have resulted from entrapment in the inflammatory tissue (acute effect), and from scarring (chronic effect).

The Immune System and Lung Cancer

Pinkerton (*CA 19*) investigated the effect of an experimental animal's immunocompetence on the carcinogenicity of benzo(a)pyrene. After the subcutaneous administration of an adjuvant (Freund's complete, incomplete, BCG, or pertussis vaccine) to pregnant hamsters, there was an enhancement of carcinogenicity of benzo(a)pyrene in the progeny as measured by frequency of skin tumor development and weight of tumor. On the other hand, prior administration of adjuvant to pregnant and nonpregnant female hamsters resulted in diminution of tumorigenesis induced by benzo(a)pyrene in those same animals. The author postulated that induction of tumors by benzo(a)pyrene is influenced by T and B cell activity; in the pregnant and non-

pregnant hamsters in which tumor formation was reduced by treatment with adjuvant, the adjuvant elicited heightened T cell response (cell-mediated antibody) and thus suppressed tumor formation and growth. However, since T cells cannot cross the placenta, a hypothetical humoral substance proliferated by the activated T cells of the pregnant mothers may have crossed the placenta, entered the fetus, and elicited a B cell response (humoral antibody). The author suggested that this humoral antibody may have resulted in increased susceptibility to tumor formation and growth.

Aryl Hydrocarbon Hydroxylase Activity and the Role of Metabolities of Polyaromatic Hydrocarbons in the Development of Lung Cancer

Studies in Humans

Cantrell, et al. (*CA 3*) studied differences in aryl hydrocarbon hydroxylase (AHH) activity of pulmonary alveolar macrophages (PAMs) obtained from 9 healthy smokers and 5 healthy nonsmokers. These investigators found a highly significant increase in AHH activity in the PAMs from the current smokers compared to those of the nonsmokers ($P < .001$). The mean ages and age ranges of the two groups of volunteers were not described, nor were their places of residence (urban vs. rural) stated. In one volunteer, AHH activity within PAMs was observed over a period of time in which he began smoking 10 to 15 cigarettes per day; AHH activity was temporally related to the presence, absence, and duration of smoking in this individual (figure 7). The authors speculated on the role of AHH as a protective mechanism against or, in contrast, as a promoter of carcinogenicity of the inhaled polyaromatic hydrocarbons of tobacco smoke.

Studies in Animals

Welch, et at. (*CA 36*) studied the effect of cigarette smoke inhalation on pulmonary BP hydroxylase (AHH) activity in rats, and reported the following: (1) When rats were exposed to the smoke from 5 cigarettes per hour for 1 to 4 hours, an initial decrease in AHH activity at 1 hour was observed, followed by a substantial increase at 2, 3, and 4 hours (figure 8). (2) This effect was blocked by actinomycin D and puromycin (inhibitors of RNA and protein synthesis) (figure 9). (3) After

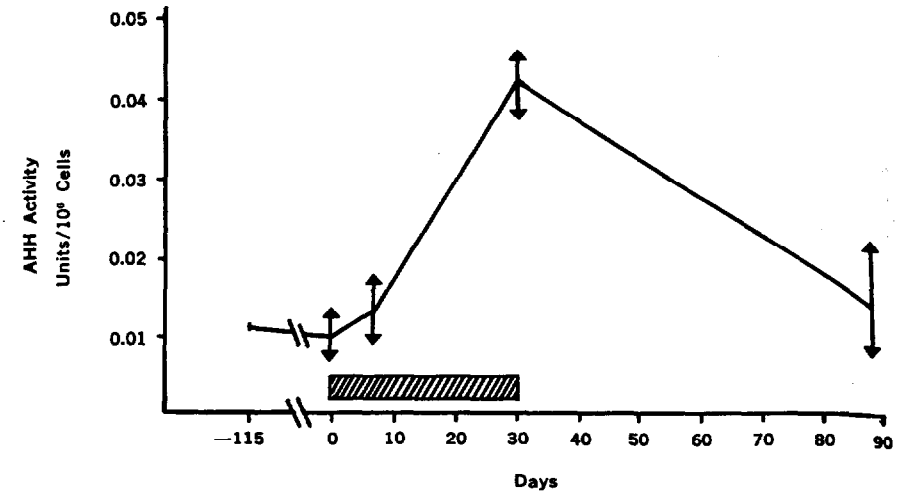

FIGURE 7.—Response of pulmonary macrophages in an individual to cigarette smoking. The shaded bar indicates duration of smoking. The vertical lines indicate the range of duplicate determinations at each time period.

SOURCE: Cantrell, E. T., et al. (*CA 5*).

4 hours of exposure to cigarette smoke, maximal AHH activity was observed at 24 hours (28-fold increase); AHH activity then dropped markedly at 6 days post-exposure, probably owing to the rapid turnover of this enzyme (figure 10) when the inducing hydrocarbons were removed from the lung. (4) In experiments in which the duration of exposure to cigarette smoke was altered, AHH activity increased with increased duration of exposure (figure 11); with as little as a 30-second exposure, at 24 hours a twofold increase in AHH activity was observed. This is in agreement with the observations of Miller and Gelboin, in Gelboin, et al. (*CA 7*), who utilized hamster embryo cells and noted that short exposure to benzo(a)anthracene (2 minutes) resulted in elevations of AHH activity for at least 12 hours. If the metabolites of polyaromatic hydrocarbons are important in pulmonary carcinogenesis, the results of these experiments lend evidence to support the hypothesis that these metabolites would be formed in increased concentrations in the lungs of smokers, and thus would lead to increased risk of tumor formation in smokers. If, on the other hand, the metabolites were noncarcinogenic, the increase in AHH activity may be looked on as a protective device against untoward effects on the parent compound (*CA 34*).