The relationship between pulmonary infection and AHH activity was investigated by Nettesheim, et al. (*CA 16*) who found that at 10 days post-inoculation of influenza virus, AHH activity was reduced in mouse lung tissue to 20 percent of control levels.

Flesher and Sydnor (*CA 6*) reported the synthesis of 6-hydroxymethylbenzo(a)pyrene by incubation of benzo(a)pyrene with rat liver homogenates as a result of enhanced AHH activity. This metabolite was carcinogenic; it produced sarcomas in rats when injected subcutaneously, as did injection of benzo(a)pyrene and 6-methylbenzo(a)pyrene. No control rats were utilized. The authors postulated that methylation and/or hydroxymethylation may be a key step in the metabolism of benzo(a)pyrene, and that the products thus formed may be potent carcinogenic agents in vivo. The fact that 100 percent of the injected rats developed sarcomas, and that no sham treated or solvent injected rats (controls) were utilized, limit the conclusions which may be drawn from this study.

Flaks, et al. (*CA 5*) demonstrated that the 7-hydroxymethyl-12-methyl and 12-hydroxymethyl-7-methyl derivatives of 7,12-dimethylbenz(a)anthracene showed similar carcinogenic potencies to the parent compound. In testing for the carcinogenicity

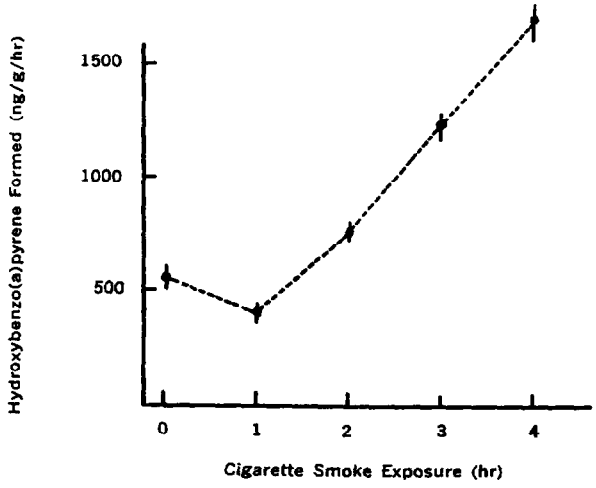

FIGURE 8.—Effect of cigarette smoke on benzo(a)pyrene-hydroxylase activity in rat lung. Four rats were placed in a chamber and exposed continuously to smoke from 5 cigarettes per hour for various time periods. After exposure, the rats were killed and the lungs were examined for benzo(a)pyrene-hydroxylase activity. The data are representative of 4–5 experiments (mean ± SE).

SOURCE: Welch, R. M., et al. (*CA 56*).

of these compounds, these investigators utilized the mouse lung explant experimental model.

Nitrogen dioxide is a known component of cigarette smoke. Palmer, et al. (*CA 18*) found no change in AHH activity of tracheobronchial mucosa of rabbits after exposure to 5, 20, and 50 p.p.m. of NO_2.

ORAL CANCER

Introduction

In the United States, oral cancers comprise approximately 2.5 percent of all cancers reported. These include cancer of the oropharynx, lip, tongue, hard and soft palate, floor of the mouth, gingiva, alveolar mucosa, and buccal mucosa. The relationships of cigarette and pipe/cigar smoking to the development of oral cancer are summarized below:

1. Prospective and retrospective studies have shown an association between mortality for oral cancer and tobacco usage in men and women.

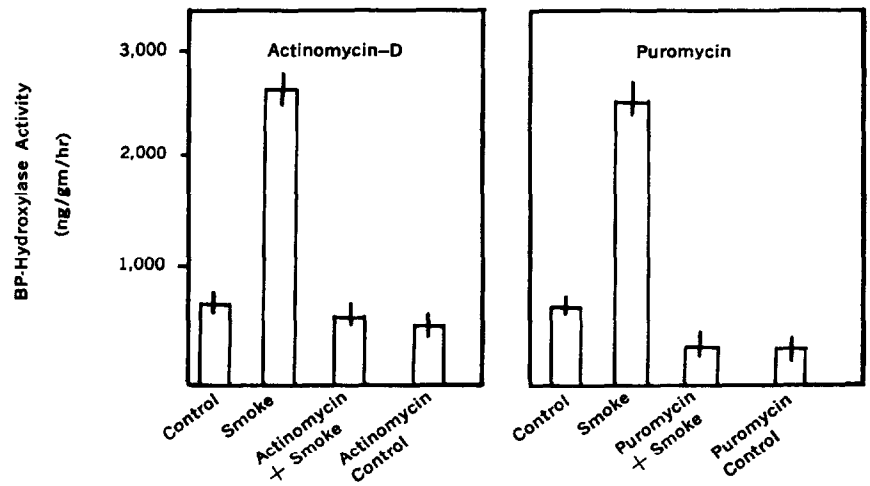

FIGURE 9.—Effect of actinomycin and puromycin pretreatment on the induction of benzo(a)pyrene-hydroxylase by cigarette smoke in the rat. Rats were treated with actinomycin or puromycin and exposed to cigarette smoke for 4 hours. Benzo(a)pyrene-hydroxylase was measured in lung immediately after exposure. Results represent the mean ± SE from 4 rats.

SOURCE: Welch, R. M., et al. (*CA 56*).

2. This association has been demonstrated for all different modes of tobacco usage—cigarette and pipe/cigar smoking, tobacco and snuff chewing, reverse smoking, and "pan" chewing.

3. Several studies have shown that the development of recurrent oral cancers has a highly significant correlation with continued smoking.

4. Tobacco usage may act in concert with alcohol consumption to increase the risk of development of oral cancer.

5. The association between tobacco use and oral cancer in both men and women has been demonstrated for Caucasian, Indian, and Asian populations.

6. Epidemiologic data suggest that premalignant lesions in the oral cavity (e.g., leukoplakia) are associated with tobacco usage.

7. Results from experimental studies indicate that cigarette smoke may contain tumor promoters active in oral carcinogenesis and is a promoting agent in the hamster cheek pouch.

Epidemiologic Studies

In a study of 483 patients with cancer of the mouth and pharynx selected from three New York City VA hospitals, Rothman and Keller (*CA 21*) found that the relative risks of development of

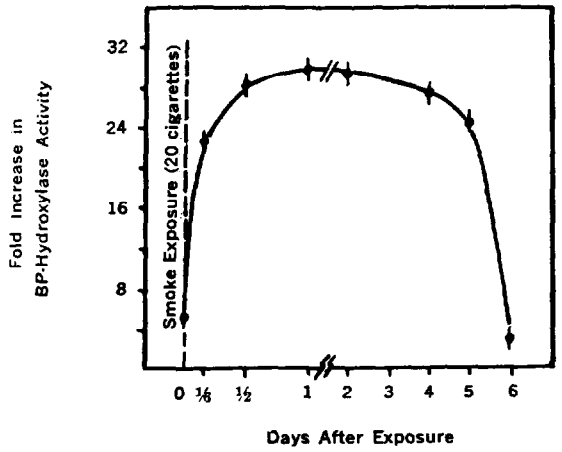

FIGURE 10.—Time course for maximum induction of benzo(a)pyrene-hydroxylase in lung after exposure of rats to cigarette smoke. Rats were exposed to cigarette smoke from 20 cigarettes (4 hours) and killed at various times after exposure. The activity of benzo(a)pyrene-hydroxylase was determined at various intervals after exposure. Each point represents the mean ± SE from 3 rats.

SOURCE: Welch, R. M., et al. (*CA 36*).

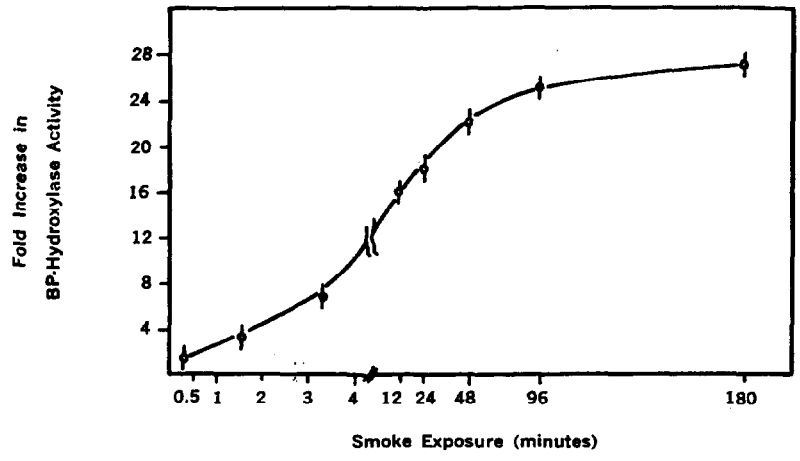

FIGURE 11.—The relationship between lung benzo(a)pyrene-hydroxylase activity and the duration of exposure to cigarette smoke in the rat. Rats were exposed to cigarette smoke from 30 seconds to 180 minutes and killed 24 hours after exposure; the lung benzo(a)pyrene-hydroxylase was measured. Each result represents the mean ± SE from 3 rats.

SOURCE: Welch, R. M., et al. (*CA 36*).

these cancers were higher for men who consumed either tobacco or alcohol than for nonsmokers and nondrinkers. When both tobacco and alcohol consumption were present, dose-response relationships for combinations of the two were demonstrated (table 2). The data presented strongly suggest that both independent and additive effects of tobacco and alcohol consumption were operative in the development of these oral cancers. The authors concluded that the increases in the relative risks of development of these oral cancers produced by smoking and alcohol consumption were additive and, therefore, independent.

Ramanathan, et al. (*CA 20*) examined 407 medical attendants and health workers in Malaysia for evidence of oral precancerous lesions. The authors found significant relations between

TABLE 2.—*Relative risk* of oral cancer according to level of exposure to smoking and alcohol*

		Smoking (cigarette equivalents/day)			
		0	<20	20–39	40+
Alcohol (oz./day)	0	1.00	1.52	1.43	2.43
	<0.4	1.40	1.67	3.18	3.25
	0.4–1.5	1.60	4.36	4.46	8.21
	1.6+	2.33	4.13	9.59	15.5

*Risks are expressed relative to a risk of 1.00 for persons who neither smoked nor drank.
SOURCE: Rothman, K., Keller, A. (*CA 21*).

tobacco smoking ($P < .05$) and mixed habit (smoking, chewing, and/or drinking) ($P < .001$), and the prevalence of oral precancerous lesions in Malay men. Significant differences in the prevalence of oral precancerous lesions were also observed between Indian men with smoking, chewing, and mixed habit and those without these habits. Many oral precancerous lesions were found among women who used tobacco, but the control group of women was too small to make statistically significant comparisons.

Lee, et al. (*CA 13*) retrospectively studied 356 men with squamous cell carcinoma of the oral cavity, matching 316 of these patients with controls of similar age and smoking habits. They concluded that alcohol consumption was significantly correlated with development of oral cancer. They then took 96 of the matched pairs who had similar drinking habits and found no differences in smoking habits.

CANCER OF THE ESOPHAGUS

1. Prospective and retrospective studies have shown a relationship between cigarette smoking and mortality from esophageal carcinoma in men and women.

2. Dose-response relationships have been demonstrated for this association.

3. These relationships have been observed in Caucasian, Asian, and American Indian populations.

4. The effect of cigarette smoking on esophageal cancer mortality rates has been shown to be independent of and synergistic with the effect of alcohol consumption.

5. Experimental data show that benzo(a)pyrene can induce esophageal cancer in mice.

PANCREATIC AND GASTRIC CANCER

1. Data from prospective and retrospective studies of men and women have demonstrated an association between smoking and mortality from pancreatic cancer.

2. Dose-response relationships have been shown for this association.

3. No firm relationship between stomach cancer and cigarette smoking has been established.

Wynder, et al. (*CA 40, 41*), in a retrospective study of 100 men and 42 women with adenocarcinoma of the pancreas, found a significantly higher percentage of male cigarette smokers (P

<.025), female cigarette smokers (P <.05), male cigarette and pipe/cigar smokers (P <.025), and male cigar smokers (P <.025) in the pancreatic cancer group than in the age, sex, and race-matched controls. For male cigarette smokers, a dose-response relationship was demonstrated for numbers of cigarettes consumed in the pancreatic cancer group (figure 12). The number of cases of women smokers with pancreatic cancer was too small to draw statistically significant conclusions with regard to dose-response relationships. Patients who smoked cigars only had a relative risk of 3.1 compared to nonsmokers, and this was also statistically significant (P <.025). (Although the association between cigarette smoking and pancreatic cancer was significant, it was not as strong as the association between cigarette smoking and lung cancer.) Patients who smoked pipes predominantly did not demonstrate a significantly higher risk of development of pancreatic cancer than nonsmokers.

Hirayama (*CA 9*) reported on several previous studies done on Japanese populations. In a retrospective study of 454 patients

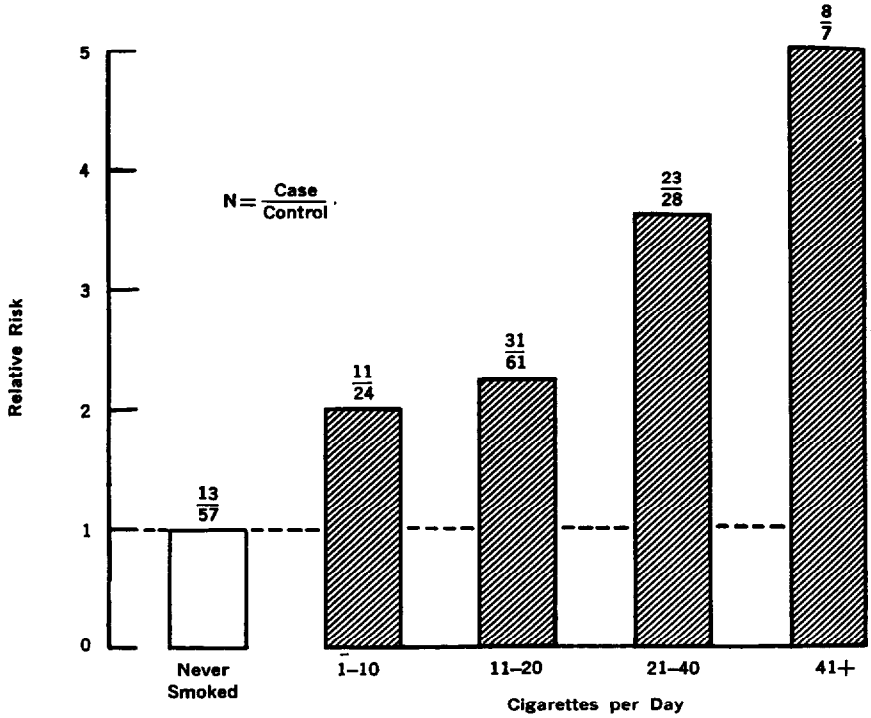

FIGURE 12.—Relative risk of pancreatic cancer by number of cigarettes smoked in males.

SOURCE: Wynder, E. L., et al. (*CA 41*).

with gastric cancer in Kanagawa prefecture from 1960 to 1961, he noted no association between smoking habits and gastric cancer. However, 67 percent of the cases were diagnosed either by X-ray or "clinical methods". In 1963, he studied six prefectures; in 1,524 patients with gastric cancer, there was "no striking association" between smoking habit and gastric cancer. In 1965, Hirayama began his prospective study of 265,118 adults. Analysis of the 3-year follow-up data revealed a higher death rate from gastric carcinoma for males who smoked cigarettes and drank hot green tea. In addition, the age-standardized death rate from gastric carcinoma for male smokers was 128 per 100,000 compared to 85 for nonsmokers; mortality ratios for male smokers:nonsmokers were 1.51. Differences between female smokers and nonsmokers were minimal. The author suggested that, in future studies, a detailed examination of the possible relationships between cigarette smoking and gastric cancer be performed.

CANCER OF THE LARYNX

1. The epidemiologic, autopsy, and experimental data which suggest a strong association between cancer of the larynx and smoking habits have been reviewed in past editions of this report. No new data have been presented within the past year which significantly add to our knowledge of the association between smoking and laryngeal cancer.

CANCER OF THE GENITOURINARY SYSTEM

Introduction

1. The association between cancer of the urinary bladder and kidney and cigarette smoking has been reviewed in previous editions of this report. No new epidemiologic data has been published within the last 12 months which amplifies our knowledge of this association.

2. Data from experimental studies dealing with tryptophan metabolism have demonstrated that metabolites of tryptophan can be carcinogenic in the bladders of mice. These metabolites are found in increased amounts in the urine of patients with non-occupational bladder carcinomas. Some data show an effect of cigarette smoking on tryptophan metabolism, while other data have not shown such an effect.

Epidemiologic Study

Thomas (*CA 30*), in a retrospective study on cytologic and histologic abnormalities of the uterine cervix, reported a significant association between current smoking habits and the incidence of carcinoma in situ ($P < .05$), with a relative risk for smokers being 1.71 ($P < .05$). The "adjusted" risk for smokers was 1.47 times that of the nonsmokers. Intensity and duration of smoking were not analyzed; ex-smokers were also not accounted for. The controls consisted of a hospitalized group of patients with normal cervical smears and may have contained a higher percentage of smokers than the population as a whole. Further epidemiologic studies are needed for full investigation of the relationship between cigarette smoking and development of carcinoma in situ of the uterine cervix, as suggested by this study.

Experimental Studies

Humans

Schievelbein, et al. (*CA 23*) reported no significant differences in the excretion of various urinary metabolites of tryptophan between smokers and nonsmokers, nor between patients with bladder carcinoma (also smokers) and those without this carcinoma. Problems in the design of this study limit the conclusions which may be drawn from the data.

Animals

Wagle and Lee (*CA 33*) found a 2 percent incidence of transitional cell bladder tumors in rats whose bladders were implanted with pellets of cigarette smoke condensate. A total of 23 percent of the rats developed squamous metaplasia.

SUMMARY OF RECENT FINDINGS ON THE RELATIONSHIP OF SMOKING AND CANCER

1. Recent epidemiologic evidence confirms the finding that cigarette smoking is the major cause of lung cancer for both men and women.
2. Current evidence suggests that, even in the presence of a possible genetic susceptibility to the development of lung cancer, cigarette smoking remains the major cause of lung cancer.

3. Results from several studies demonstrated a dose-response relationship between smoking and oat cell carcinoma; a major prospective study demonstrated such a relationship for well-differentiated squamous cell carcinoma, oat cell carcinoma, and adenocarcinoma.
4. The current epidemiologic data suggest that the incidence of lung cancer in women continues to rise. The rising incidence of lung cancer in women correlates well with the increasing trends in smoking among women.
5. Present data are conflicting with regard to dose-response relationships for cigar and pipe smokers and the development of lung cancer; the data are consistent for the fact that light cigar smokers are at a low risk of developing lung cancer.
6. Recent data confirm the synergistic effect of asbestos and smoking exposure on the risk of developing lung cancer in both men and women.
7. Results from experimental studies in hamsters continue to demonstrate that exposure to benzo(a)pyrene results in the production of respiratory tract malignancies, especially squamous cell carcinomas.
8. Data from experimental studies in animals suggest that chronic respiratory infections may enhance the carcinogenicity of components of cigarette smoke, as may alterations in the immune system.
9. Current evidence suggests that components of cigarette smoke induce AHH activity in pulmonary macrophages in humans and in pulmonary parenchymal tissue and embryo cells in animals. The role of AHH in tumorigenesis and/or as a host defense mechanism against potential carcinogens is presently unclear.
10. Recent epidemiologic data strongly indicate that cigarette smoking plays an independent role in the development of oral cancer.
11. Recent epidemiologic data confirm the association between smoking and pancreatic cancer.

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CHAPTER 3

NON-NEOPLASTIC BRONCHOPULMONARY DISEASES

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NON-NEOPLASTIC BRONCHOPULMONARY DISEASES

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) (defined here as chronic bronchitis and emphysema) accounted for approximately 25,000 deaths in the United States in 1969. In 1970, in the U.S., the combined prevalence of chronic bronchitis for members of both sexes over age 17 was 29.5 per 1,000 population, and for emphysema was 9.8 per 1,000 population. In 1970, persons with chronic bronchitis lost, on the average, 1.4 workdays per year, and those with emphysema lost greater than 5 workdays per year due to disability from these diseases.

Epidemiologic, autopsy, and experimental data presented in previous editions of this report (1964, 1967, 1968, 1969, 1971, 1972, 1973) indicate that cigarette smoking is the primary cause of chronic bronchitis and emphysema. A summary of that evidence is presented below:

1. Results from numerous prospective studies show a markedly increased mortality from COPD for male smokers compared to nonsmokers. There is a limited amount of data dealing with the relationship between cigarette smoking and COPD mortality in women.

2. Dose-response relationships between cigarette smoking and mortality from chronic bronchitis and emphysema were demonstrated in all studies in which dose-specific mortality rates were evaluated. Heavy cigarette smokers ran relative risks of mortality from chronic bronchitis ranging from 3.6 to 21.2 times those of nonsmokers, and relative risks of mortality from emphysema ranging from 6.9 to 25.3 times those of nonsmokers.

3. Data from many studies demonstrate that male and female smokers suffer from symptoms of COPD (including cough, sputum production, and dyspnea) more frequently than do nonsmokers.