cigarette, the average length of time taken to smoke a cigarette (except in the highest number of puffs category), and the taking of more puffs at the end of the cigarette.

These findings, and those of the study of Auerbach, et al. (*11*), add further support to the dose-response relationship between lung cancer and total cigarette smoke condensate exposure.

Summary and Conclusions

1. Epidemiological evidence derived from a number of prospective and retrospective studies coupled with experimental and pathological evidence confirm the conclusion that cigarette smoking is the main cause of lung cancer in men. These studies reveal that the risk of developing lung cancer increases with the number of cigarettes smoked per day, the duration of smoking, and earlier initiation, and diminishes with cessation of smoking.

2. Cigarette smoking is a cause of lung cancer in women but accounts for a smaller proportion of cases than in men. The mortality rates for women who smoke, although significantly higher than for female nonsmokers, are lower than for men who smoke. This difference may be at least partially attributed to difference in exposure; such as, the use of fewer cigarettes per day, the use of filtered and low "tar" cigarettes, and lower levels of inhalation. Nevertheless, even when women are compared with men who apparently have similar levels of exposure to cigarette smoke, the mortality ratios appear to be lower in women.

3. The risk of developing lung cancer among pipe and/or cigar smokers is higher than for nonsmokers but significantly lower than for cigarette smokers.

4. The risk of developing lung cancer appears to be higher among smokers who smoke high "tar" cigarettes or smoke in such a manner as to produce higher levels of "tar" in the inhaled smoke.

5. Ex-cigarette smokers have significantly lower death rates for lung cancer than continuing smokers. There is evidence to support the view that cessation of smoking by large numbers of cigarette smokers would be followed by lower lung cancer death rates.

6. Increased death rates from lung cancer have been observed among urban populations when compared with populations from rural environments. The evidence concerning the role of air pollution in the etiology of lung cancer is presently inconclusive. Factors such as occupational and smoking habit differences may also contribute to the urban-rural difference observed. Detailed epidemiologic surveys have shown that the urban factor exerts a small influence compared to the overriding effect of cigarette smoking in the development of lung cancer.

7. Certain occupational exposures have been found to be associated with an increased risk of dying from lung cancer. Cigarette smoking interacts with these exposures in the pathogenesis of lung cancer so as to produce very much higher lung cancer death rates in those cigarette smokers who are also exposed to such substances.

8. Experimental studies on animals utilizing skin painting, tracheal instillation or implantation, and inhalation of cigarette smoke or its component compounds, have confirmed the presence of complete carcinogens as well as tumor initiators and promoters in tobacco smoke. Lung cancer has been found in dogs exposed to the inhalation of cigarette smoke over a period of more than two years.

CANCER OF THE LARYNX

Cancer of the larynx is a disease which predominantly affects males in the 55 to 70 year age group. In 1967, a total of 2,468 males and 329 females died of laryngeal cancer in the United States. With the development and application of more effective therapy during the past 30 years, the death rate for cancer of the larynx appears to be dropping slightly (*282, 289*) ; however, the incidence continues to rise. Figures from the Connecticut Cancer Registry (*88*) show that the age-adjusted incidence per 100,000 population of cancer of the larynx for males rose from 3.0 in 1950 to 5.6 in 1961.

Epidemiological Studies

A number of epidemiological studies have investigated the relationship between smoking habits and the development of cancer of the larynx. The major prospective studies, as outlined in table 20, show that smokers of cigarettes run an approximately six-to-tenfold risk of dying from this form of cancer as compared to nonsmokers. Smokers of pipes and cigars incur a three-to-sevenfold risk. The retrospective studies listed in table A21 uniformly show fewer nonsmokers and more smokers among cases with cancer of the larynx than among matched controls. Table A22 summarizes the relative risk ratios derived from the retrospective studies. The wide variation is due to a number of factors, including type of population and interview technique. But, in general, the magnitude of most of these ratios is of the same order as in the prospective studies.

Wynder, et al. (*312*) have distinguished between cancer of the intrinsic and extrinsic larynx. Tumors arising on the vocal cords are classified as intrinsic and constitute approximately 70 percent of the lesions. The extrinsic larynx is composed of those sections of the larynx excluding the vocal cords and may also be referred to as

TABLE 20.—*Laryngeal cancer mortality ratios*

(Actual number of deaths shown in parentheses)[1]
SM = Smokers. NS = Nonsmokers.

Prospective studies							
Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of laryngeal cancer deaths	Cigarettes/day	Pipes, cigars	Comments
Hammond and Horn, 1958, U.S.A. (*120*).	187,783 white males 50–69 years of age in 9 states.	Questionnaire and follow-up of death certificate.	3½	24 SM . .24 NS . . 0	Cigarette smokers 17/24.	*Cigar* 3/24 *Mixed* 4/24	Data referring to mortality ratio included cancer of esophagus and mouth.
Doll and Hill, 1964, Great Britain (*74*).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	16 SM . .16 NS . . 0	*All smokers by amount in grams* NS . . . . 1–14 . . . . . 1.00 15–24 . . . . . 1.00 >25 . . . . . 7.50	*Pipe and cigar*† NS . . . . 1.00 SM 5.00	† Includes data on ex-smokers of pipes and cigars. No NS died of laryngeo-tracheal cancer, therefore 1–14 gram SM set as 1.00 standard. Data combine laryngeal and tracheal carcinoma.
Kahn (Dorn), 1966, U.S.A. (*159*).	U.S. male veterans, 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	54 SM . .51 NS . . 3	NS . . . . . 1.00 (3) 1–9 . . . . . 3.27 (1) 10–20 . . . . . 8.45(10) 21–39 . . . . . 13.62(11) >39 . . . . . 18.85 (3) All . . . . . 9.95(25)	*Pipe* NS . . . . 1.00 (3) SM . . . . 10.33 (6) *Pipe and cigar* NS . . . . 1.00 (3) SM . . . . 7.28(11)	Refers to current cigarette smokers only.
Hammond, 1966, U.S.A. (*118*).	440,558 males 562,671 females 35–84 years of age in 25 states.	Interviews by ACS volunteers.	4	57 SM . .54 NS . . 3	NS . . . . . 1.00 (3) SM (age 45–64) . . 6.09(32) SM (age 65–79) . . 8.99(18)	*Pipe and cigar* NS . . . . 1.00 (3) SM 3.37 (4)	Male data only. Pipe and cigar data refer to males 55–84 years of age.

TABLE 20.—*Laryngeal cancer mortality ratios (cont.)*

(Actual number of deaths shown in parentheses)[1]

SM — Smokers. NS = Nonsmokers.

Prospective studies								
Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of laryngeal cancer deaths	Cigarettes/day		Pipes, cigars	Comments
Weir and Dunn, 1970, U.S.A. (*306*).	68,153 males in various occupations in California.	Questionnaire and follow-up of death certificate.	5–8	11 SM . . 11 NS . . 0	NS . . . . . — ±10 . . . . . 1.00 ±20 . . . . . 5.99 >30 . . . . . 5.84			No nonsmokers died of laryngeal carcinoma, therefore ±10 smoker set as 1.00 standard. NS includes pipe and cigar smokers. SM includes ex-smokers.

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

the hypopharynx. These authors noted that the percentage of heavy smokers among the patients with cancer of both the extrinsic and intrinsic larynx was significantly greater than that among controls. However, it is of interest that the excess risk of laryngeal cancer among cigar and pipe smokers in this study could be attributed to the extrinsic laryngeal group.

As in studies of oral cancer, it appears that alcohol consumption should also be taken into account in studies of laryngeal cancer. Wynder, et al. (*312*) reported a significantly increased risk of extrinsic cancer among those with alcohol intake above 7 ounces of whiskey per day. With less than this amount, no increased risk was evident. Schwartz, et al. (*248*), noted no effect in relation to alcohol intake. Further research into the interaction of these two variables is necessary.

Pathological Study

Auerbach, et al. (*9*) studied histological changes in the larynges of 942 men, age 21 to 95, who were autopsied at a single hospital between 1964 and 1967. Cases of primary cancer of the larynx were excluded from the study. Smoking histories for all cases were obtained from family members of the deceased by trained interviewers. The randomized histological sections were graded by one observer. Tables A23 and A24 summarize the findings in the true vocal cord. Of the men who never smoked, 75 percent had no cells with atypical nuclei, only 4.5 percent had sections with areas containing 60 to 69 percent of cells with atypical nuclei, and none had a higher percentage. The 116 ex-smokers had laryngeal histology similar to that of the nonsmokers, as far as atypical nuclei were concerned. However, disintegrating nuclei were found in 40.5 percent of the ex-cigarette smokers and in only 0.4 percent of the remaining cases. Only one of the 91 cigar and or pipe smokers had no atypical cells. Three had carcinoma *in situ*, and one case had a section showing early invasive primary carcinoma.

The highest percentage of atypical cells was found among the cigarette smokers. The proportion of cases with a high degree of cellular change increased with increased daily smoking. None of the pack-or-more-a-day smokers was free of atypical nuclei in the laryngeal epithelium. Of those who smoked two or more packs per day, 85 percent had lesions with 60 percent or more atypical cells as compared to 1 percent of the nonsmokers. Between 10 and 18 percent of the cigarette smokers had areas of carcinoma *in situ*, and 4 of the 644 cases showed early microscopic invasion. The thickness of the basal level of the true vocal cord was also directly related to the amount smoked.

Experimental Study

Dontenwill (*76*) has recently reported the development of an effective and practicable method by which small rodents (hamsters, rats, mice) can be exposed to long-term passive inhalation of cigarette smoke in a manner which circumvents the fatal effects of acute toxicity which ruined earlier attempts but allows for a dosage of smoke great enough to induce the development of chronic pathological changes. The Syrian Golden hamster was found to be the most suitable species for such inhalation experiments for several reasons: its resistance to pulmonary infections, its resistance to the effects of nicotine as compared to that of rats or certain strains of mice, and, especially, its susceptibility to develop tracheobronchial cancers after treatment with carcinogens, in contrast to its almost total freedom from the spontaneous development of these tumors.

Dontenwill demonstrated that the concentration of deposited cigarette smoke was greatest in the hamster's larynx as compared to the other portions of the exposed respiratory tract (table 25), and that the laryngeal epithelium was the tissue which underwent the greatest smoke-induced histological changes.

In studying the changes in the larynx, the author differentiated five stages of epithelial change, using as his reference the Atlas of Tumor Pathology of the Armed Forces Institute of Pathology (*5*). Table 26, quoted by Dontenwill, describes the five types of change. They range from benign, such as epithelial hyperplasia, to premalignant, exemplified by pseudoepitheliomatous leukoplakia.

The results of the inhalation experiment are presented in figure 4 in which a dosage-related increase in the severity of the epithelial changes is represented in graphic form. The author also reported, and depicted with photomicrographs, the finding of an early invasive squamous cell carcinoma. This form of cancer is the predominant type involving the human larynx.

Summary and Conclusions

1. Epidemiological, experimental, and pathological studies support the conclusion that cigarette smoking is a significant factor in the causation of cancer of the larynx. The risk of developing laryngeal cancer among cigarette smokers as well as pipe and/or cigar smokers is significantly higher than among nonsmokers. The magnitude of the risk for pipe and cigar smokers is about the same order as that for cigarette smokers, or possibly slightly lower.

2. Experimental exposure to the passive inhalation of cigarette smoke has been observed to produce premalignant and malignant changes in the larynx of hamsters.

TABLE 25.—*Deposition of ^{14}C-labeled smoke particles in particular regions of the respiratory tract*[1]

Organ	Traced radio-activity (nCi)	Organ	Estimated radio-activity (nCi)	Deposition of particles (%)	Proportional area of the respiratory tract	Traced deposition in relation to the proportional area
Head and palate	6.11	Head, palate	5.5	37.4		
Tongue	0.41	Oral cavity in total.	1.6	10.9		
Larynx	0.39				0.1–0.3	X561–187
Trachea	0.26		7.6 (traced)	51.7	0.6	X62.3
Lungs	6.95				1000	X1
Total	14.12		[2]14.7	100.0		

[1] Cigarettes labeled with ^{14}C-1-n-hexadecan; data represent mean values from 10 animals, calculated from surface distribution in the head.

[2] The value of 14.7 contains 0.58 nanocuries as estimated from quantity of deposition in the nontraced oral cavity regions (calculated as to proportional area).

SOURCE: Dontenwill, W. (76).

TABLE 26.—*Classification of the five registered stages of epithelial changes at the larynx*[1, 2]

Stage	Acanthosis (thickening of stratum spinosum multicellular layer)	Hyperkeratosis increased cornification (stratum corneum)	Parakeratosis (incomplete cornification of nuclei in the stratum corneum)	Dyskeratosis (premature atypical cornification changes in the nucleus proliferation of the basal layer)	Mitosis
1. Pachydermia (epithelial hyperplasia)	+	+	†	†	†
2. Leucoplakia	+	+	‡	‡	‡
3. Verrucous leucoplakia	+	+	+	‡	‡
4. Papillomatous leucoplakia	+	†	†	++	‡
5. Pseudoepitheliomatous leucoplakia	+	+	+	+++	+

[1] Symbols: † = negative; ‡ = minimal; + = weak; ++ = medium; +++ = strong.
[2] From Atlas of Tumor Pathology of the Armed Forces Institute of Pathology.
SOURCE: Adapted from Dontenwill, W. (*76*).

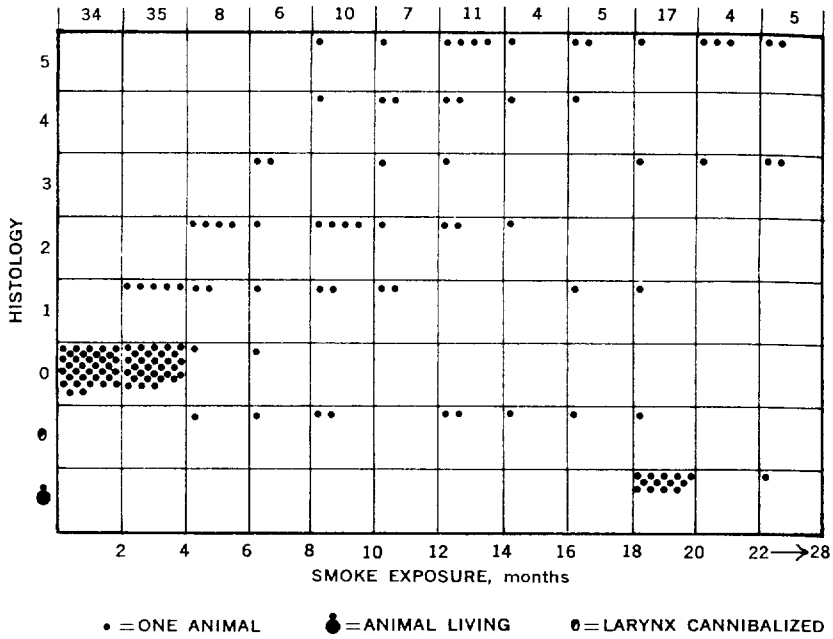

FIGURE 4.—Effects of chronic cigarette smoke inhalation on the hamster larynx. Review of the results of the inhalation experiments: number of smoke-exposed animals with and without changes in the larynx, duration of smoke exposure, and number of animals still alive.
SOURCE: Dontenwill, W. (*76*).

ORAL CANCER

The cancers included in this category are those of the lips, tongue, floor of the mouth, hard and soft palate, gingiva, alveolar mucosa, buccal mucosa, and oropharyns. It is estimated that 15,000 of these cancers will be diagnosed in the United States in 1970, accounting for about 2.5 percent of the estimated 600,000 malignant neoplasms reported (*289*). A variety of histological types of malignant neoplasms can affect these tissues, but squamous cell carcinoma is by far the predominant type, accounting for about 90 percent of the cancers.

The incidence of and mortality from oral cancers has remained steady over the past 20 to 30 years. The Connecticut Cancer Registry (*88*), which is a fairly reliable index of incidence, noted that the incidence among males remained between 15.8 and 16.3 per 100,000 population during the years from 1950–1961. Examination of mortality rates over the past 20 to 30 years (*282, 289*) reveals a similar constancy.

The apparent lack of change in mortality from oral cancer in

contrast to the sharp increase that took place in lung cancer rates in those years is probably due to several of the following factors. First, pipe and cigar smoking are both significantly related to cancer of the oral cavity, and the increase in cigarette smoking among men, noted between 1920 and 1955, has been, to a large degree, accompanied by corresponding reductions in the use of pipes and cigars. Second, aside from the various changes which the International Classification of Diseases (ICD) had undergone during that period, the diseases discussed above are recorded in ICD Codes 140–148 which include some neoplasms not found to be related to the use of tobacco. The various sites of cancer themselves do not contribute equally to the overall rate and are subject to widely different cure rates, so that their contributions to the total incidence rate is different from their contribution to the overall mortality rate from oral cancer. Although more than 20,000 cancers of the oral cavity were estimated as newly diagnosed in 1967, the total number of individuals recorded as dying from oral cancer during that year was only 6,718 (*289*).

Oral cancer occurs predominantly in people of the middle and older age groups. More than 90 percent of all oral cancers occur in persons over age 45, with the average age at time of diagnosis approximating 60. Although the majority of oral cancers occur in men, there is recent evidence that the ratio of males affected to females affected is decreasing (*257*).

Epidemiological Studies

The use of tobacco in various forms has been associated with the development of cancer of the oral cavity and pharynx. The studies in this area of concern are truly international, many having been carried out in Asian regions as well as in the West.

The major prospective epidemiological studies have found increased rates of these cancers for cigarette smokers as well as for pipe and cigar smokers (see table 27). Pipe smoking, per se, has long been recognized as a cause of lip cancer (*291*). The methodology and results of the numerous retrospective studies are summarized in tables A28 and A28a. These studies almost uniformly show significant relationships between the various forms of tobacco use and cancers of the oral cavity and pharynx.

Studies in Asian regions have examined the prevalence or incidence of premalignant change, such as oral leukoplakia, as well as that of cancer of the oral cavity. In many of these studies, forms of tobacco use not prevalent in Western countries have been investigated, including reverse smoking (in which the lighted end of the cigarette is kept in the mouth close to the palate) and the chewing

TABLE 27.—*Oral cancer mortality ratios—prospective studies*

(Actual number of deaths shown in parentheses)

SM= Smokers, NS = Nonsmokers.

Author year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths	Cigarettes	Pipes, cigars	Comments
Hammond and Horn, 1958, U.S.A. (*120*).	187,783 white males in 9 States 50–69 years of age.	Questionnaire and follow-up of death certificate.	3½	56 †SM ..51 NS .. 3	20/56	*Pipe* *Mixed* 5/56 21/56 *Cigar* 5/56	Data referring to mortality ratio do not include cancer of larynx and esophagus. † Excludes two occasional only smokers.
Doll and Hill, 1964, Great Britain (*74*).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	19 SM ..19 NS .. 0	*All smokers by amount in grams* NS ..... — 1–4 ..... 1.00 15–24 ..... 0.25 >25 ..... 5.25	*Pipe and cigar* NS ..... 1.00 SM 1.00	No NS died of oral cancer, therefore 1–14 gram smoker set as 1.00 standard.
Kahn (Dorn), 1966, U.S.A. (*139*).	U.S. male veterans, 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	61 SM ..50 NS ..11	NS ..... 1.00(11) †Cigs/day 1–9 .... 0.86 (1) 10–20 ..... 2.93(13) 21–39 ..... 7.34(20) >39 ..... 5.73 (3) All ..... 4.09(37)	*Pipe* NS ..... 1.00(11) SM ..... 3.12 (4) *Cigar* NS ..... 1.00(11) SM 4.11 (9)	Data do not include pharynx. † Refers to current cigarette smokers only.
Hammond, 1966, U.S.A. (*118*).	440,558 males 562,671 females 35–84 years of age in 25 States.	Interviews by ACS volunteers	4	95 SM ..88 NS .. 7	NS ..... 1.00 (7) SM (age 45–64) ... 9.90(63) SM (age 65–79) .. 2.93(25)	† Pipe and/or cigar. NS ..... 1.00 (7) SM ..... 4.94(15)	† Male data only. Pipe and cigar data refer to males 55–84 years of age.
Weir and Dunn, 1970, U.S.A. (*306*).	68,153 males in various occupations in California.	Questionnaire and follow-up of death certificate.	5–8	19	NS ..... 1.00 ±10 ..... 3.69 ±20 ..... 1.17 >30 ..... 5.52 All 2.76		SM includes ex-smokers. NS includes pipe and cigar smokers.

of "pan" or "Nass," which are mixtures of tobacco with either betel nut or lime ash, and other ingredients (*241, 255, 256*). Snuff dipping, a habit in which snuff is placed in the gum and retained there for prolonged periods, has also been associated with the development of oral cancer (*193, 210*), as has the chewing of tobacco (*124, 193, 241, 298*).

The risk of developing a second primary mouth or throat cancer, after the recognition of the first primary cancer, has been found to be greater in continuing smokers than in those who quit smoking. All of the patients studied by Moore (*190*) were asymptomatic for at least three years following the treatment of the first cancer. Of the 117 patients with adequate smoking histories, only 4 of 43 (9 percent) who quit smoking developed a new primary cancer. On the other hand, 27 of 74 (36 percent) who continued to smoke developed a second primary cancer.

However, a study by Castigliano (*53*) of patients treated for oral cancer did not show a greater risk of a second primary among continuing smokers. In this study, 5 of 26 (19 percent) of those patients who did not quit smoking developed a second primary cancer as compared to 9 of 51 (18 percent) of those who did quit. The rate of quitting smoking in the two studies is markedly different (36 percent in the Moore study and 62 percent in the Castigliano study). From the data presented in the two papers, it is not possible to evaluate the other significant ways in which the populations may have differed.

Keller (*140*) studied 408 males with histologically confirmed squamous cell cancer of the mouth or pharynx. This author dealt with the question of recurrent tumors in a somewhat different manner. The patients were observed for the development of a second or third primary cancer at an anatomically discrete site of the mouth and pharynx within a median period of three years after the first cancer. He found that a second or third cancer (termed a coexisting cancer) developed in 28 of the 408 cases. Among these 28 cases with 33 coexisting neoplasms, 21.7 percent were heavy smokers, but among their matched controls, there were no heavy smokers. Coexisting cancers were most commonly found on the soft palate, an anatomical site that is in direct contact with the mainstream of tobacco smoke.

More recently, Wynder, et al. (*315*) studied 63 male and 23 female patients with multiple primary cancers of the mouth and pharynx. They observed that heavy smoking prior to the development of the oral cancer was associated with a greater likelihood of developing a second primary. Also, continued smoking after the first primary was found to have a significant association with the occurrence of a second primary.

With or without smoking, use of alcohol appears to contribute to the development of oral cancer (*124, 140, 183, 297, 322*). In a study of male veterans, Keller (*140*) found that heavy smoking and heavy drinking were associated with cancer of the mouth and pharynx. No studies are presently available which determine the relative contributions and possible interactions of heavy smoking, heavy drinking, and concurrent nutritional deficiencies in the etiology of these cancers.

Experimental Studies

In 1964, the Advisory Committee to the Surgeon General on Smoking and Health (*291*) reported that cigarette smoke and cigarette smoke condensates had failed to produce cancer when applied to the oral cavity of mice and rabbits or to the palate of hamsters and that the oral mucosa appears to be resistant in general to cancer induction even when highly active carcinogens such as benzo[a]pyrene are applied. Some of the difficulties in experimental design were attributed to the fact that mechanical factors, such as secretion of saliva, interfere with the retention of applied carcinogenic agents on the tissues of the oral cavity and pharynx. Positive results with certain carcinogens have, however, been obtained in the hamster cheek pouch, but it has also been pointed out that the cheek pouch lacks salivary glands and that its structure and function differ from those of the oral mucosa. The majority of these studies are outlined in table A29.

Although cigarette smoke condensate acts as a complete carcinogen on mouse skin, the work of several authors (*319*) supports the concept that cigarette smoke contains cancer promoters that may be of special importance, particularly in oral carcinogenesis. Elzay (*90*) has reported that whole cigarette smoke is a promoting agent for the hamster cheek pouch. More importantly, regarding the chewing of tobacco, Bock, et al. (*27, 30*), Van Duuren, et al. (*294*), and Wynder and Hoffmann (*321*) have shown that unburned tobacco products contain tumor promoters that might contribute to the promoting activity of the smoke.

Roth, et al. (*226, 227*) have shown that the dye-binding capacity of the DNA of oral epithelial cells is significantly enhanced in cigarette smokers in contrast to nonsmokers, probably reflecting an increase in the DNA content of oral epithelial cells in smokers. Smokers had values of dye-binding capacity intermediate between nonsmokers and 21 patients with proven oral cancer. Those smokers who refrained from smoking for up to six months showed a significant decrease toward more normal values.

SUMMARY AND CONCLUSIONS

1. Epidemiological and experimental studies contribute to the conclusion that smoking is a significant factor in the development of cancer of the oral cavity and that pipe smoking, alone or in conjunction with other forms of tobacco use, is causally related to cancer of the lip.

2. Experimental studies suggest that tobacco extracts and tobacco smoke contain initiators and promoters of cancerous changes in the oral cavity.

CANCER OF THE ESOPHAGUS

Esophageal cancer accounted for 4,306 deaths among American males in 1967 and 1,321 deaths among females. The death rate from esophageal cancer has remained relatively constant since 1949.

EPIDEMIOLOGICAL STUDIES

The major prospective epidemiological studies (table 30) have indicated a significant relationship between smoking and esophageal cancer. Overall mortality ratios for male cigarette smokers range from 1.74 to 6.17. There are insufficient data concerning females for establishing firm conclusions.

A number of retrospective studies concerning the relationship of smoking and esophageal cancer are outlined in table A31 and A31a. Smokers incur risk ratios ranging from 1.3 to 6.6 when compared with nonsmokers.

As in studies of oral cancer, the effect of alcohol consumption must be taken into account in studies of esophageal cancer. Because a relationship between alcohol consumption and tobacco use is known to exist, Wynder and Bross (*310*) analyzed the association between tobacco consumption and esophageal cancer after adjusting for alcohol intake. They found that in the absence of alcohol consumption, there was no association between the use of tobacco and esophageal cancer but that in the presence of alcohol consumption, an increasing relative risk with increasing number of cigarettes smoked was apparent, as well as an association between cigar and pipe smoking and esophageal cancer.

More recently, Takano, et al. (*272*), in a retrospective study of 200 patients with esophageal carcinoma, found an increased risk with smoking which was magnified by increased alcohol consumption. Martinez (*183*) analyzed the association of tobacco usage and esophageal cancer after controlling for age, sex, and alcohol consumption. Increasing relative risks with increasing tobacco use

TABLE 30.—*Esophageal cancer mortality ratios—prospective studies*

(Actual number of deaths shown in parentheses)[1]

SM = Smokers. NS = Nonsmokers.

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of esophageal cancer deaths	Cigarettes/day	Pipes, cigars	Comments
Hammond and Horn, 1958, U.S.A. (*120*).	187,783 white males in 9 States 50–69 years of age.	Questionnaire and follow-up of death certificate.	3½	34 NS ... 1 SM ... 33	Cigarette smokers 15/33.	*Pipe* 2/33 *Cigar* 2/33 *Mixed* cigarette smokers 13/33	Data referring to mortality ratios included cancer of mouth and larynx.
Doll and Hill, 1964, Great Britain (*74*).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	29	*All smokers by amount in grams* NS ..... 1.00 1–14 .... 2.00 15–24 .... 3.50 >25 ..... 5.00 All 3.00	†*Pipe and cigar* NS .... 1.00 SM 2.00	†Includes ex-smokers of pipe and cigars.
Kahn (Dorn), 1966, U.S.A. (*139*).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	111 NS ... 11 SM ...100	NS ..... 1.00(11) †1–9 ..... 1.76 (2) 10–19 .... 4.71(18) 20–39 ....11.50(24) >25 ..... 7.65 (3) All ..... 6.17(47)	*Pipe* 1.99 (3) *Cigar* 5.33(12)	† Refers to cigarette smoking only.
Hammond, 1966, U.S.A. (*118*).	440,558 males 562,671 females 35–84 years of age in 25 States.	Interviews by ACS volunteers.	4	46 NS ... 6 SM ... 40	NS ..... 1.00 (6) SM (age 45–64) . 4.17(32) SM (age 65–79) . 1.74 (8)	*Pipe and Cigar* NS .... 1.00 SM .... 3.97(14)	

TABLE 30.—*Esophageal cancer mortality ratios—prospective studies (cont.)*

(Actual number of deaths shown in parentheses)

SM = Smokers. NS = Nonsmokers.

Author year, country, reference	Number and type of population	Data collection	Follow-up years			Comments
Hirayama, 1967, Japan (*125*).	265,118 male and female adults 40 years of age and older.	Trained PHS nurse interview and follow-up of death certificate.	1½	SM ... 21	NS ..... 1.00 ($p<0.01$) SM 2.47 (21)	Refers to all forms of smoking.
Weir and Dunn, 1970, U.S.A. (*306*).	68,153 males in various occupations in California.	Questionnaire and follow-up of death certificate.	5–8	32	NS ..... 1.00 ±10 ..... 1.27 ±20 ..... 1.69 >30 ..... 1.82 All 1.82	NS includes pipe and cigar smokers.

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

were noted. The consumption of very hot beverages was also found to be related to the development of esophageal cancer.

Pathological Study

Autopsy studies of smokers as compared with nonsmokers, specifically observing the pathological changes in esophageal tissue, have been performed by Auerbach, et al. (*15*). A microscopic study was made of 12,598 sections of esophageal autopsy tissue from 1,268 men who died from causes other than esophageal cancer. The findings were strikingly similar to the abnormalities generally accepted as representing premalignant tissue changes in the respiratory tract epithelium. Esophageal epithelial cells with atypical nuclei (having an irregular distribution of chromatin) were found far more frequently in cigarette smokers than in nonsmokers. Basal cell hyperplasia and hyperactive glands were also found more frequently in cigarette smokers than in nonsmokers. An increase in frequency with amount of cigarette smoking was noted for both epithelial cells with atypical nuclei and basal cell hyperplasia. Tables A32 and A33 summarize these findings.

Experimental Studies

Kuratsune, et al. (*156*) investigated the possibility that the carcinogens known to be present in tobacco smoke could penetrate the esophageal epithelium more readily if dissolved in aqueous ethanol. Mice were exposed to several compounds by esophageal intubation. Tissues were then removed and studied by fluorescence microscopy. Deeper penetration and a different distribution were found when B[a]P was dissolved in aqueous ethanol as compared to B[a]P in olive oil. It was also found that benzo[a]anthracene and fluoranthene dissolved in ethanol solution or aqueous caffeine solution could penetrate the epithelium of the esophagus.

Horie, et al. (*132*) reported on the development of 10 papillomas and one squamous cell carcinoma of the esophagus in a group of 63 mice periodically forced to drink a solution of benzo[a]pyrene dissolved in diluted ethanol. Twenty-six papillomas and one squamous cell carcinoma also developed in a group of 63 mice to which 4-nitroquinoline 1-oxide was administered in the same way. None of the 67 control animals given only diluted ethanol developed neoplasms.

Several other authors have reported nitrosamine-induced esophageal cancer in experimental animals (*56, 79, 80, 81*). As noted above, the presence of nitrosamines in cigarette smoke is still a subject of debate.

Summary and Conclusions

1. Epidemiological studies have demonstrated that cigarette smoking is associated with the development of cancer of the esophagus. The risk of developing esophageal cancer among pipe and/or cigar smokers is greater than that for nonsmokers and of about the same order of magnitude as for cigarette smokers, or perhaps slightly lower.

2. Epidemiological studies have also indicated an association between esophageal cancer and alcohol consumption and tthat alcohol consumption may interact with cigarette smoking. This combination of exposures is associated with especially high rates of cancer of the esophagus.

CANCER OF THE URINARY BLADDER AND KIDNEY

Epidemiological Studies (Bladder)

Cancer of the urinary bladder accounted for 6,019 deaths among American males and 2,743 deaths among American females in 1967 (*289*). Incidence rates have increased from 1949 to 1962 (*88*), but the death rates from bladder cancer have remained relatively stable during that period. Improvements in early diagnosis and therapy may have masked the increasing incidence of this disease.

A number of epidemiological studies have indicated that smokers have an increased risk of contracting or of dying from bladder cancer (see tables 34 and A35). Certain of these studies include kidney cancer mortality in the results. The major prospective studies, with the exception of that of British physicians, have shown bladder cancer mortality ratios among cigarette smokers ranging from 1.40 to 2.89. Smokers of more than 1 pack per day were shown to incur ratios of 3.42 to 5.41. The study by Doll and Hill (*74, 75*) of British physicians, on the other hand, reports death rates for smokers to be lower than those of nonsmokers based on 38 bladder cancer deaths. The mortality ratios for pipe or cigar smokers are substantially lower than those among cigarette smokers. Pipe smokers were shown by both Hammond and Horn (*120*) and Kahn (*139*) to incur ratios approximating 1.20.

Retrospective studies (table A35a) have also shown an increased proportion of smokers among bladder cancer patients when compared with matched controls. Relative risk ratios for bladder cancer among smokers range from 1.0 to 7.3 among all smokers and up to 10.3 among heavy smokers of all types.

TABLE 34.—*Kidney and urinary bladder cancer—prospective studies—Mortality ratios*

(Actual number of deaths shown in parentheses)[1]

SM = Smokers. NS = Nonsmokers.

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths	Cigarette/day	Pipe, cigar	Kidney	Bladder	Comments
Hammond and Horn, 1958, U.S.A. (*120*).	187,783 white males in 9 States.	Questionnaire and interview.	3½	287 SM .249 NS .. 38	NS .... 1.00(38) <10 ... 2.00(14) 10–20 .. 2.00(42) >20 ... 3.42(41)	*Pipe* NS ...1.00(38) SM ...1.17(21) *Cigar* NS ...1.00(38) SM ...1.06(19)			Data include patients dying of prostatic carcinoma. Data refer to microscopically proven carcinomas.
Doll and Hill, 1964, Great Britain (*74*).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	38		NS ...1.00 SM ...0.41		*All SM by amount in grams* NS ...1.00 1–14 ..0.59 15–24 ..0.65 >25 ...0.76 All 0.71	
Best, 1966, Canada (*21*).	Approximately 78,000 male Canadian veterans.	Questionnaire and follow-up of death certificate.	10	114	NS .... 1.00 <10 ... 1.33(29) 10–20 .. 1.44(57) >20 ... 1.43(15) All .... 1.40(10)	*Pipe* NS ...1.00 SM ...0.56(10) *Cigar* NS ...1.00 SM ...1.16 (3)			Refers to genitourinary cancers as a group.
Hammond, 1966, U.S.A. (*118*).	440,558 males 562,671 females 35–84 years of age in 25 States.	Interviews by ACS volunteers.	4	*Bladder* 138 SM .115 NS .. 23 *Kidney* 104 SM . 82 NS .. 22		*Cigarettes* NS .....1.00(22) SM (age 45–64) ...1.42(54) SM (age 65–79) ...1.57(28)	*Cigarettes* 1.00(23) 2.00(59) 2.96(56)		*Male data only.* Bladder includes other urinary tract cancers.

TABLE 34.—*Kidney and urinary bladder cancer—prospective studies—Mortality ratios (cont.)*

(Actual number of deaths shown in parentheses)[1]

SM = Smokers. NS = Nonsmokers.

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths	Cigarette/day	Pipe, cigar	Kidney	Bladder	Comments
Kahn (Dorn), 1966, U.S.A. (*139*).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	*Bladder* 224 SM .172 NS .. 52 *Kidney* 141 SM ..102 NS .. 39		NS .....1.00 (39) Pipe .....1.32 (6) Cigar .....0.77 (6) Cigarettes/day: 1–9 .....0.97 (4) 10–19 .....1.34 (21) 20–39 .....1.68 (16) >39 .....2.75 (5) All 1.45 (46)		1.00 (52) 1.20 (8) 0.94 (10) 1.10 (6) 1.93 (37) 3.20 (34) 2.52 (5) 2.15 (82)	Bladder includes other urinary tract cancers.
Hirayama, 1967, Japan (*135*).	265,118 male and female adults 40 years of age and older.	Trained PHS nurse interview and follow-up of death certificate.	1½	SM 6	NS .... 1.00 SM 10.00 (6)				Bladder cancer only. Refers to all forms of smoking.
Weir and Dunn, 1970, U.S.A. (*396*).	68,153 males in various occupations in California.	Questionnaire and follow-up of death certificate.	5–8	*Bladder* 27 *Kidney* 27			NS ...1.00 ±10 ..0.86 ±20 ..3.30 >30 ..2.57 All ...2.46	NS ...1.00 ±10 ...1.52 ±20 ...2.81 >30 ...5.41 All 2.89	SM include ex-smokers. NS include pipe and cigar smokers.

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

Epidemiological Studies (Kidney)

A total of 5,894 Americans died of cancer of the kidney during 1967. A relationship between smoking and this type of cancer has been suggested by several epidemiological studies. The three major studies which separately examine the relationship of kidney cancer to smoking (table 34), namely those of Hammond (*118*), Kahn (*139*), and Weir and Dunn (*306*), have shown mortality ratios for all cigarette smokers to range from 1.42 to 2.46. Retrospective studies by Bennington, et al. (*18, 19*) have indicated a significant association between all forms of smoking and renal adenoma and adenocarcinoma.

Experimental Studies

Numerous experiments have been undertaken by many investigators to elucidate the relationship of tobacco smoking to bladder carcinogenesis. The two areas of major concern have centered upon the presence of a known bladder carcinogen, beta naphthylamine, in cigarette smoke and the presence of abnormal tryptophan metabolism in patients with bladder cancer.

By virtue of data gathered concerning industrial exposure of workers, beta naphthylamine has long been known as a bladder carcinogen. Complementing such data was the work of Hueper, et al. (*136*) who subjected mongrel dogs to daily subcutaneous injections and oral administration of commercial beta naphthylamine. Thirteen of the 16 animals developed bladder papillomas and carcinomas of the bladder. Saffiotti, et al. (*236*) fed hamsters a diet containing up to 1.0 percent beta naphthylamine and observed that 18 of 39 animals developed bladder tumors, almost all typical transitional cell carcinomas. More recently, Conzelman, et al. (*59*) administered beta naphthylamine to 24 rhesus monkeys for more than 30 months. Transitional cell carcinomas of the urinary bladder were induced in 9 of the animals, and a dose-response relationship was apparent.

Pailer, et al. (*207*) and Miller and Stedman (*185*) failed to find this amine in cigarette smoke. However, more recently, Hoffmann, et al. (*127*) identified it in cigarette smoke. The authors, noting the minute quantity present in each cigarette (2.2×10^{-9}g), hesitated to attach a biological significance to the finding.

Of more recent interest have been the metabolites of tryptophan present in certain patients with bladder cancer. A number of normal and abnormal metabolites of tryptophan have been found to be carcinogenic when tested by implantation in the bladders of mice. These include 3-hydroxykynurenine (OHKy), 3-hydroxyanthranilic

acid (OHA), 3-hydroxy-2-amino-acetophenone (all orthoaminophenols), the 8-methyl ether of xanthurenic acid (CHXa), xanthurenic acid (Xa), L-kynurenine (Ky), quinaldic acid, and 3-methoxyanthranilic acid (3CHOA) (*2, 36, 37, 39, 47, 48*). OHKy and OHA are frequently present in human urine, as is kynurenic acid (KyA).

Certain investigators have concentrated their attention on the presence of abnormal tryptophan metabolites and increased amounts of normal tryptophan metabolites in the urine of patients with bladder cancer as compared with selected controls (*1, 40, 46, 97, 148, 214, 243, 329*). These authors have observed the increased excretion of Ky, KyA, OHKy, anthranilic acid, OHA, and acetylkynurenine in such patients. Yoshida, et al. (*329*), in a recent study concerning the relationship between tryptophan metabolism and heterotopic recurrences of human urinary bladder tumors, reported that those patients with recurrences showed abnormal metabolite excretion more often than those without recurrences.

The relationship of smoking to these biochemical findings is presently uncertain. Kerr, et al. (*143*), in 30 experiments on 3 smokers and 3 nonsmokers who were given large doses of tryptophan, found that smoking increased the urinary excretion of OHKy and OHA and decreased that of N'methylnicotinamide (an end product of tryptophan metabolism). Kerr concluded that smoking interferes with the normal metabolism of tryptophan. Recently, Brown, et al. (*45*) studied 15 adults under smoking and abstinence conditions and found that except for the basal excretion of acetylkynurenine, tryptophan metabolite excretion did not change with smoking or cessation. The authors also compared 13 nonsmokers and 17 regular cigarette smokers under basal and tryptophan-loaded conditions. No differences were observed in the excretion of the measured tryptophan metabolites. However, due to its instability, OHA was not measured. The authors concluded that the relationship of smoking to urinary bladder cancer was probably not via its effect on the kynurenine pathway of tryptophan metabolism.

Another experimental approach to the relationship of smoking and urinary bladder cancer is reflected in the work of Schlegel, et al. (*244, 245*). The authors observed an elevated concentration of certain ortho-aminophenols in the urine of bladder cancer patients and cigarette smokers, when compared with nonsmokers (*244*). More recently (*245*), the same group compared the chemiluminescence of the urines of smokers, nonsmokers, and bladder tumor patients. They noted that nonsmokers showed the lowest level of luminescence (which they relate to the presence of aromatic hydrocarbons) and the bladder tumor patients the highest level. The normal cigarette smokers' level was found to be intermediate.

TABLE 36.—*Pancreatic cancer mortality ratios—prospective studies*

(Actual number of deaths shown in parentheses)[1]

SM = Smokers. NS = Nonsmokers.

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths	Cigarettes	Pipes, cigars	Comments
Best, 1966, Canada (*21*).	Approximately 78,000 male Canadian veterans.	Questionnaire and follow-up of death certificate.	6	SM ... 35	*Current (cigarettes only)* NS ..... 1.00 <10 .... 1.40 (5) 10-20 ... 1.96 (16) >20 .... 2.37 (7)	*Pipes* NS ..1.00 SM ..2.60 (6) *Cigars* NS ..1.00 SM ..2.63 (1)	
Hammond 1966 U.S.A. (*118*).	440,558 males 562,671 females 35–84 years of age in 25 States.	Interviews by ACS volunteers.	4	262 SM ...233 NS ... 29	NS ..... 1.00 (29) SM (age 45–64) 2.69 (158) SM (age 65–79) 2.17 (75)		Male data only.
Kahn (Dorn) 1966 U.S.A. (*139*).	U.S. male veterans, 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	344 †SM ...256 NS ... 88	NS ..... 1.00 (88) 1–9 .... 0.87 (8) 10–20 ... 1.93 (65) 21–39 ... 2.18 (43) >39 .... 1.87 (7) All 1.84 (125)	*Pipes* NS ..1.00 (88) SM ..0.74 (8) *Cigars* NS ..1.00 (88) SM ..1.52 (27) *Both* NS ..1.00 (88) SM ..0.93 (13)	† Refers to current smokers of all types.
Hirayama, 1967, Japan (*125*).	265,118 male and female adults 40 years of age and older.	Trained PHS nurse interview and follow-up of death certificate.	1½	SM ... 14	NS ..... 1.00 SM .....15.56 (14) } ($p<0.01$)		
Weir and Dunn, 1970, U.S.A. (*306*).	68,153 males in various occupations in California.	Questionnaire and follow-up of death certificate.	5–8	SM ... 71	NS ..... 1.00 ±10 .... 2.94 ±20 .... 2.45 >30 .... 1.44 All 2.43		SM includes ex-smokers. NS includes pipe and cigar smokers.

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the ex-

At present, no definite conclusions can be drawn concerning the interrelationships of bladder cancer, abnormal tryptophan metabolism, and tobacco smoking. Further study is required in this and the other areas of bladder cancer pathophysiology.

Summary and Conclusions

1. Epidemiological studies have demonstrated an association of cigarette smoking with cancer of the urinary bladder among men. The association of tobacco usage and cancer of the kidney is less clear-cut.

2. Clinical and pathological studies have suggested that tobacco smoking may be related to alterations in the metabolism of tryptophan and may in this way contribute to the development of urinary tract cancer.

CANCER OF THE PANCREAS

Several prospective epidemiologic studies have suggested a relationship between cigarette smoking and cancer of the pancreas (table 36). A retrospective study of 465 cases of pancreatic cancer by Ishii, et al. (*137*) has shown a dose-related increased risk of pancreatic cancer in association with smoking. Analysis of dietary data revealed that the relative risk for pancreatic cancer from smoking was considerably greater than from dietary factors.

No experimental studies relating to this question have been reported.

Summary and Conclusions

Epidemiological studies have suggested an association between cigarette smoking and cancer of the pancreas. The significance of the relationship is not clear at this time.

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