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

Investigator and reference	Cigarettes	Pipes	Cigars	Chewing	Miscellaneous
Broders (41)	(Lip)−	(Lip)+	(Lip)−	(Lip)+.	
Lombard and Doering (221).		(Oral)+			
Bigelow and Lombard (26)					(All forms combined—oral)+
Ebenius (103)	(Lip)− [2]	(Lip)+		(Lip)−.	
Levin et al. (207)	(Lip)−	(Lip)+	(Lip)±.		
Mills and Porter (237)	(Oral)±				(Pipes and cigars combined—oral)+.
Moore et al. (245)	(Lip, mouth)− [3]	(Lip, mouth)−		(Lip, mouth)+	(Snuff—lip, mouth)+.
Sadowsky et al. (301)	(Lip, tongue, other oral, pharynx)−.	(Lip, tongue, other oral)+	(Tongue, other oral)+.		
Sanghvi et al. (306)	(Oropharynx)+ [3]			(Oral)+	(If smoke and chew—base of tongue, hypopharynx)+.
Ledermann (202)	(Oral)+.				
Wynder et al. (378)	±M, +F (Floor of mouth)	(Each site except tongue)+	(Each site)+	(Gingiva, lip)±.	
Schwartz et al. (314)	(Pharynx)+ [4]	(Oral)−.			
Wynder et al. (388)	M−, F+ (Oral and pharynx).	(Lip)+	M+, F+ (oral and pharynx).		
Wynder et al. (385)	(Pharynx)+, (Other sites)−		(Tongue, gingiva, pharynx)+.		(Pipes, and cigars combined tongue)+.
Peacock et al. (272)				(Oral)+ [5]	(Snuff—oral)+.[5]
Staszewski (326)	(Lip, oral cavity)+				(Pipes and cigars combined—lip, oral cavity)±.
Vogler et al. (355)					(All forms combined)+, F+ (snuff—lip and buccal cavity in both cases).

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

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

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

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

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

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

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

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

Carcinogenesis

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

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

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

Pathology

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

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

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

Evaluation

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

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

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

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

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

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

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

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

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

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

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

Conclusions

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

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

Laryngeal Cancer

Epidemiologic Evidence

RETROSPECTIVE STUDIES

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

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

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

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

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

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

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

Investigator and year	Reference	Country	Sex	Cases		Controls		Collection of data
				Number	Method of selection	Number	Method of selection	
Stasrewski 1960.	(327)	Poland	M F	207 13	Patients admitted to chronic disease hospital during 1957 & 1958 with histologically confirmed squamous-cell carcinoma of the larynx. 0.5% non-smokers 87.9% cigarettes only 1.9% pipes and/or cigars 88.4% "heavy smokers" 96.1% inhalers 30.8% smoke, F	M 912 F 1813	Patients admitted during 1957 & 1958 to chronic disease center for cancerous and non-cancerous conditions presumably not related to tobacco consumption. 17.3% non-smokers 60.5% cigarettes only 11.1% pipes and/or cigars 49.0% "heavy smokers" 66.8% inhalers 8.4% smoke, F	Author interviewed patients suspected of lung cancer for smoking history and background.

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

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

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

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

PROSPECTIVE STUDIES

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

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

Carcinogenesis

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

Pathology

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

Evaluation of the Evidence

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

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

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

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

TIME TRENDS

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

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

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

SEX DIFFERENTIAL IN MORTALITY

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

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

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

LOCALIZATION OF LESIONS

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

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

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

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

Conclusion

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

Esophageal Cancer

Epidemiologic Evidence

RETROSPECTIVE STUDIES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Investigator, year, and reference	Percent non-smokers		Percent heavy smokers		Percent inhalers among smokers		Relative risk; ratio to non-smokers	
	Cases	Controls	Cases	Controls	Cases	Controls	All smokers	Heavy smokers
Sadowsky et al. 1953 (301)	3.8	13.2					4.0	
Sangvhi et al. 1955 (306)	5.5	17.3	Average number of bidis smoked				3.6	
			15.3	14.1				
Wynder et al. 1957 (385):								
M	13	24					2.1	
F	about 85	about 92					2.0	
Staszewski 1960 (326, 327)	0	18	95.8	59	87.5	80		16
Schwartz et al. 1961 (315)	3	17	Total amount smoked daily (cigarettes)		39	38	6.6	
			16.8	16.0				
Wynder and Bross 1961 (374):								
(1) American males	5	15	48	33			3.4	1.8
(2) American females	41	78	27	16			4.1	1.9
(3) Indian males	13	28					2.6	
(4) Indian females	78	94					4.5	

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

PROSPECTIVE STUDIES

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

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

Carcinogenesis

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

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

Evaluation of Evidence

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

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

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

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

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

Conclusion

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

Urinary Bladder Cancer

Epidemiologic Evidence

RETROSPECTIVE STUDIES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

PROSPECTIVE STUDIES

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

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

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

Carcinogenesis

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

Evaluation of the Evidence

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Conclusion

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

Stomach Cancer

Epidemiologic Evidence

RETROSPECTIVE STUDIES

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