Long-term continuous oxygen therapy in hypoxemic patients with chronic airway obstruction has been noted to have a beneficial effect of reducing pulmonary arteriolar resistance (*30*).

It is pertinent to note at this point that there is a developing body of experimental evidence discussed in previous Reports and in this chapter that cigarette smoking may have acute deleterious effects on airway resistance and pulmonary vasoconstriction which can be especially harmful to the patient whose pulmonary function is already compromised. The disordered pulmonary ventilation-perfusion relationships and pulmonary hypertension found in some patients with severe chronic bronchitis can only be worsened by further bronchoconstriction and possibly by pulmonary vasoconstriction caused by continued cigarette smoking. These can enhance cardiopulmonary decompensation and lead to heart failure from cor pulmonale.

Further research is necessary to clarify more precisely the interrelationships between the disturbances of ventilation-perfusion caused by chronic obstructive bronchropulmonary diseases and cardiovascular abnormalities as they relate to cigarette smoking.

SUMMARY AND RESEARCH SUGGESTIONS

Additional evidence compiled since 1967 confirms previous positive findings and extends our knowledge about some of the effects of cigarette smoking on pulmonary function. There has been further clarification of some of the interrelationships between chronic obstructive bronchitis and adverse cardiopulmonary effects indicating that pulmonary hypertension and cor pulmonale may result from the more severe forms of chronic obstructive bronchopumonary disease. Smoking is a major cause of chronic bronchopulmonary disease and in addition may have particularly harmful cardiopulmonary effects in those patients with severe chronic obstructive bronchitis.

Research suggestions: (1) Long-term followup studies on changes in pulmonary function among continuing cigarette smokers as compared to those who have never smoked cigarettes and those who have discontinued cigarette smoking. (2) Longitudinal studies of relatively young people prior to the initiation of smoking in order to compare pulmonary function before and after the taking up of smoking.

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CHAPTER 3

Smoking and Cancer

Contents

315-131 O—68——7

INTRODUCTION

The primary purpose of the 1968 Supplemental Report is to review the pertinent literature that has become available subsequent to the 1967 Report. Brief mention of the conclusions of the 1964 Report and the highlights of the 1967 Report is made to facilitate an understanding of the significance of the most recent information.

The current research findings should be considered in the perspective of the research evidence previously reported in the 1964 (*91*) and 1967 (*92*) Reports.

Conclusions of the 1964 Report (*91*)

Lung Cancer

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

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

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

Oral Cancer

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

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

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.

Cancer of Urinary Bladder

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

Stomach Cancer

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

Highlights of the 1967 Report (*92*)

Lung Cancer

1. Aditional epidemiological, pathological, and experimental data not only confirm the conclusions of the Surgeon General's 1964 Report regarding lung cancer in men but strengthen the causal relationship of smoking to lung cancer in women.

2. Cessation of cigarette smoking sharply reduces the risk of dying from lung cancer relative to the risk of those who continue.

3. Although additional experimental studies substantiate previous experimental data, additional research is needed to specify the tumor-initiating and tumor-promoting agents in tobacco smoke and to elucidate the basic mechanisms of the pathogenesis of lung cancer.

Laryngeal Cancer

The conclusion of the Surgeon General's 1964 Report that cigarette smoking is a significant factor in the causation of laryngeal cancer in the male is supported by additional epidemiological evidence.

Other Cancers

Additional evidence supports the conclusions of the Surgeon General's 1964 Report and indicates a strong association between various forms of smoking and cancers of the bucal cavity, pharynx, and esophagus. In the absence of further information concerning the interaction of smoking with other factors known or suspected as causative agents, further conclusions cannot be made at this time, although a causative relationship seems likely.

Additional epidemiological, clinical, and experimental data strengthen the association between cigarette smoking and cancer of the urinary bladder, but the presently available data are insufficient to infer that the relationship is causal.

GENERAL ASPECTS OF CARCINOGENESIS

Since the 1967 report, recent advances in the tobacco chemistry field were reviewed in two articles (*65*, *82*). The characterization of tobacco smoke by gas chromatography and digital computer opened a new avenue for the exploration of tobacco smoke. The first preliminary data indicate the presence of several thousands of compounds in tobacco smoke. This number far exceeds the 700–800 compounds presently identified (*23*).

The 1967 Report discussed the major concepts of experimental tobacco carcinogensis. A recent monograph by Wynder and Hoffmann (*104*) thoroughly describes and analyzes experimental carcinogenesis as it relates to tobacco and tobacco smoking. The reduction of tumorigenicity is of particular concern. This can be accomplished by: (1) reduction of total "tar" content, and (2) reduction of specific tumori-

genic agents. It has been well established that experimental tumor production is dose-related to the amount of "tar" in cigarette smoke condensate (*7*). The amount of "tar" yield varies with parameters such as: (1) type of tobacco, (2) curing and processing, and (3) filtration. It has been demonstrated that by selecting, curing and blending as well as by using specific filter materials and cigarette paper, one can significantly reduce the "tar" yield of mainstream cigarette smoke (*39,83,88*).

Over the past 15 years there has been a general decrease in the amount of "tar" and nicotine content of cigarettes (*96, 104*). One reason probably is the decreased nicotine and "tar" content in the "lighter" tobaccos now being grown. Another is the increased public demand for "filtered" cigarettes.

Increased nitrate content of tobacco and the addition of nitrate to cigarettes has been reported to reduce the tumor yield in experimental animals (*104*). Smoke from air-cured tobacco is less tumorigenic than flue or sun-cured tobacco (*96, 104*) and cigarettes using more sheets and stems rather than whole leaf have been shown to be less tumorigenic (*64,104*).

Also, more porous cigarette paper (*70*), and the addition of nitrate, citrate, or phosphate to cigarette paper increases the burning rate of the cigarette, thereby lowering the number of puffs taken per unit of cigarette (*104*).

Filtration will decrease the total "tar" yield (*61, 63, 96, 104*), but except for the phenolic component, commerical filters do not selectively filter specific carcinogenic components from the "tar".

It has been shown that "tars" of tobacco extracts have increasing carcinogenic properties in direct relationship to the temperature of pyrolysis (*104*).

It is important to note that tobacco extract itself contains relatively high amounts of tumor promoters. The tumor promoting activity of tobacco extracts is of the same magnitude as that of tobacco smoke condensate (*104*) but so far no clear tumorigenic relationship is evident between them (*6*).

N-Nitrosamines

Despite recent publications on the presence of N-nitrosamines in tobacco (*76*) and cigarette smoke (*55*), the present evidence must be regarded as insufficient because of the high probability that this is artifactual (*66*). The studies described so far have failed to identify these agents in fresh tobacco smoke (*45, 66*). However, since several of the N-nitrosamines are strong carcinogens (*58*) and tobacco smoke contains several dozen secondary amines and oxides of nitrogen which may be precursors for nitrosamines (*66, 76, 80, 105*), tobacco smoke should be regarded as a potential source of N-nitrosamines.

Polonium-210

New data on polonium-210 in tobacco leaf and cigarette smoke have originated from various countries (*8*, *13*, *26*, *27*, *28*, *51*, *52*, *68*, *89*). The polonium-210 values vary between 1–50 picocuries per 1.0 g. tobacco; 30–50 percent of it is recoverable in the mainstream smoke of cigarettes without filter tips. Using special filter material, up to 90 percent of the polonium-210 can be filtered out of the mainstream smoke (*8*). One major source for polonium-210 in tobacco was reported to be phosphate fertilizer (*89*). Analyses of human tissues demonstrated that lung, blood, and liver of smokers contain higher concentrations of polonium-210 than the corresponding organs of nonsmokers (*27*, *40*, *41*, *57*, *68*). Rajewsky et al. (*68*) estimate a daily polonium-210 inhalation rate of 2 picocuries for a smoker of 20 cigarettes per day. Their autopsy studies indicate an alpha dose exposure for the basal cells of the subsegmental and terminal bronchi of 41 mrem and 79 mrem per year, respectively, in smokers of 20 cigarettes per day. In view of the fact that Jacobi (*44*) calculated a dose rate in these same basal cells of 1–2 rem per year from the decay of naturally occuring radon and thoron in the air, Rajewsky, et al. (*68*) consider it unlikely that cancer is caused by the inhalation of polonium-210, in tobacco smoke. In a review of the role of radioactive substances on the effect of smoking, Casarett was of a similar opinion (*14*).

Selenium

At present there is still no substantial evidence implicating selenium as a respiratory carcinogen, although this is still somewhat disputed (*29*, *100*, *101*).

Tobacco Pesticides and Growth Inhibitors

The most widely used sucker growth inhibitor is maleic hydrazide. This agent was recently reported to be carcinogenic (*25*). Tobacco leaf and cigarette smoke are known to contain organic pesticides (*32*, *104*). The first identified carcinogenic pesticide in tobacco and cigarette smoke is 1,1-dichloro-2-(o-chlorophenyl)-2-(p-cholorophenyl) ethane (o,p'-DDD) (*38*, *56*), which is a technical by-product of the commercial insecticide p,p'-DDD. At present there is no known evidence of chlorinated insecticides contributing to tobacco carcinogenesis.

Possible Fungal Contamination of Tobacco

The mold *Aspergillus flavus* is known to synthesize the carcinogens of the aflatoxin group (*17*). However, a recent investigation reported

the absence of these agents in tobacco and cigarette smoke (*90*). Nevertheless, further studies are indicated to evaluate the possibility that some tobaccos may be contaminated with carcinogens produced by fungi.

EXPERIMENTAL ASPECTS OF CARCINOGENESIS

Passive Inhalation of Tobacco Smoke

In attempting to reproduce lung cancer in experimental animals, the limitations of presently available bioassays, mainly passive inhalation studies, have been discussed in the previous Reports (*91*, *92*). Large scale studies in which a variety of animals have been exposed to the passive inhalation of tobacco smoke have essentially failed in producing squamous cell cancer of the lung (*104*).

The difficulties with passive inhalation studies in animals relate in part to the toxicity of carbon monoxide and nicotine. The defensive "filtration" capabilities of the nasal passages and the epithelium of the upper respiratory tract, necessitate relatively high exposure levels, which in the case of tobacco smoke cannot adequately be accomplished by passive inhalation methodologies.

Some laboratory studies failed to produce squamous cell cancer in C57 black mice even though some of the animals were previously inoculated with Swine influenza virus (*106*). Harris and Negroni (*35*), in experiments with C57 black mice, some of which were inoculated with viruses, achieved some enhancement of adenocarcinoma, but did not produce any proven squamous cell cancers.

Long-term cigarette smoke exposures in hamsters led only occasionally to tracheal papillomas and not to squamous cancer (*20*). However, one could sensitize these animals with diethylnitrosamine and enhance the tumor production initiated by this carcinogen by a variety of volatile irritants including tobacco smoke.

Active Inhalation of Tobacco Smoke

Active tobacco smoke inhalation studies as reported in the 1967 Report (*92*) have shown that hyperplastic and metaplastic changes can be produced in the lungs of dogs. These studies are expensive and it is difficult to keep the dogs alive long enough to permit the expected development of neoplastic transformation. Auerbach, et al. (*4*) in continuing experiments with "smoking" dogs, have shown all the bronchial epithelial changes including dysplasia, which is the most advanced stage of pre-malignant change. More research is needed to elucidate the biomechanisms involved in the pathogenesis of lung cancer caused by tobacco smoking.

LUNG CANCER

Mortality

The annual number of deaths in the United States from cancer of the lung (ICD Code 162, 163) increased from 18,313 deaths in 1950 to 48,483 in 1965 (*95*). During the same period of time the crude death rate rose from 12.2 deaths per 100,000 population to 25.0 deaths per 100,000 population. The lung cancer age-adjusted mortality rate for males increased from 18.5 per 100,000 population in 1950 to 39.2 per 100,000 population in 1965; while in the females, the age-adjusted rates increased from 3.9 to 6.4 per 100,000 population over the same period.

The age-specific death rates for males show an increase with age up to the 65 to 74 year age group, and then a decline. On the other hand, the female lung cancer death rates show a relatively steady increase with age, averaging approximately 7 additional deaths per 100,000 population between each ten year age group. As a result, the male to female mortality ratio varies from a low of 2.0 for the 25 to 34 year age age group, to a high of 8.5 for the 65 to 74 year age group.

TABLE 1.—*Death rates per 100,000 population for lung cancer, by age and sex, 1965*

Sex	25–34 years	35–44 years	45–54 years	55–64 years	65–74 years	75–84 years	85 years and over
Males	1. 2	13. 2	58. 2	159. 2	269. 3	226. 4	152. 7
Females	0. 6	4. 4	13. 7	22. 1	31. 6	36. 5	45. 6
Ratio M/F	2. 0	3. 0	4. 2	7. 2	8. 5	6. 2	3. 3

SOURCE: National Center for Health Statistics (*95*).

Retrospective Studies

Studies in Iceland uniquely support the evidence that the increase in lung cancer is related to the increase in cigarette consumption. Iceland is a small country with a total population of about 200,000. There is relatively little air pollution, due mainly to the use of hot water springs instead of the combustion of fuel as a source of heating. Dungal (*21*) in 1950 noted a beginning rise in lung cancer in Iceland, associated with the rise in cigarette consumption during and after World War II. He predicted that if the cigarette consumption continued to rise, the 20 to 30 year lag in lung cancer death rates would begin to become apparent during the decade 1960–1970. Thorarinsson, et al. (*87*) reported a large increase in the lung cancer incidence in Iceland from 1931 to

1964, corresponding to a marked increase in per capita cigarette sales. The average annual incidence of lung cancer during the 10–year period, 1955–1964, was 12.1 in men and 6.5 in women per 100,000 population. However, comparing the first and second 5–year intervals, there was a 30 percent increase in lung cancer incidence in men and a 52 percent increase in women (table 2).

TABLE 2.—*Average annual incidence rates for cancer of the lung, by sex: Iceland, 1955 to 1964*

[Rate per 100,000 population]

Sex	1955–59	1960–64	1955–64
Males	10. 3	13. 6	12. 1
Females	5. 1	7. 8	6. 5

SOURCE: Thorarinsson, H. et al. (*57*).

Although the total number of deaths was small, 88 percent of the histologically classifiable tumors were of the squamous, undifferentiated, or oat-cell varieties. Ninety percent of the squamous, 82 percent of the oat-cell cancers, and 33 percent of the undifferentiated or adenocarcinomas occurred in smokers.

A small study by Guillan, et al. (*31*) again illustrates that cigarette smoking is also associated with adenocarcinoma of lung cancer. Of 24 cases of adenocarcinoma of the lung in men, a smoking history could be determined in 22 cases. Of these, 91 percent were smokers.

In a large retrospective study of 1,787 lung cancer patients in Japan by Ishikawa (*42*), adenocarcinoma was the most frequent histologic type noted in both males and females who did not smoke. Squamous cell carcinoma was the most frequent histologic type in male cigarette smokers and undifferentiated carcinoma the most frequent type in female cigarette smokers.

Of the male and female lung cancer patients, 22.6 and 2.9 percent, respectively, were smokers of over 30 cigarettes a day. Ishikawa compared this to the corresponding smoking habits of patients in a large ongoing prospective study of Hirayama (discussed later) which showed only 4.3 percent of the adult males over age 40 and 0.1 percent of the adult females over age 40 smoking 30 cigarettes a day or more.

Abelin, et al. (*1*) showed that the relative risk of lung cancer in Switzerland was associated with heavy cigar and pipe smoking (as well as cigarette smoking) to a much greater degree than previously reported. Most other studies have not shown a high association of lung cancer with cigar and pipe smoking. The authors suggest that their findings might be due to differences in either the amount smoked and/

or the carcinogenicity of Swiss and German cigars as compared to American cigars. The difference might also be explained by the greater use and more frequent inhalation of small cigars in Switzerland as compared to other countries where larger cigars are more commonly smoked but rarely inhaled.

Prospective Studies

The major, long-term, prospective studies were reviewed in the 1967 Report. The Doll and Hill (*18*, *19*) study is still in progress, but no new data have become available. Data collection for the Best, Hammond, and Dorn studies (*5*, *34*, *46*) are completed, but various aspects are still being analyzed and new information will appear in the future.

Preliminary data from a large scale prospective study (*37*) of 265,118 men and women in Japan show that the death rate from lung cancer is significantly higher in cigarette smokers as compared to nonsmokers for both males and females. There is also a positive correlation between lung cancer death rates and both the amount smoked and the

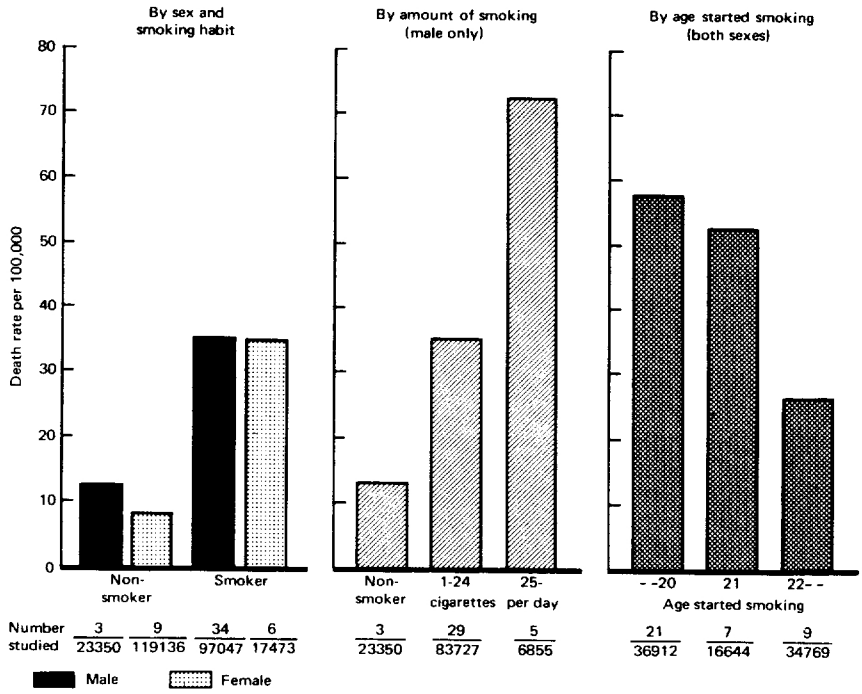

FIGURE 1—Death rates for lung cancer, among persons age over 40 years, classified by sex and extent of cigarette smoking, and by age smoking began: Study of 29 Health Center Districts in Japan, January 1966 to March 1967.

SOURCE: Hirayama, T. (37)

age smoking began, but the number of deaths is too small for adequate analysis at this time.

Lung Cancer Relationships in Women

Critics have tried to throw doubt on the smoking-lung cancer relationship by saying that the lung cancer death rates for women have increased only slightly as compared to the greater relative increase in the number of women smokers.

It is true that the lung cancer death rates for women are presently much lower than the corresponding rates for men. Women presently account for only about one-sixth of the total deaths from lung cancer. But since 1930 the lung cancer death rate in women has increased over 400 percent. Over the past 14 years alone this increase has been over 50 percent (*94*). A most likely reason for the difference in male/female lung cancer death rates is that women still have not had the same degree of total exposure to cigarettes as have men. For instance, as late as 1955, only 24.5 percent of the adult female population (age 18 and over) were regular smokers compared to 52.6 percent of the adult male population (*33*). In 1966 the figures show only 33.6 percent of the adult females smoking (age 21 and over) as compared to 51.8 percent of the adult males. Also, the female smoker's per capita consumption was about 26 percent less than that of the male smoker in 1955, and about 20 percent less in 1966 (*93*). In addition, it has been shown that women smoke differently than men do (*99*). They do not smoke cigarettes as far to the end, where proportionally more nicotine and "tars" are inhaled than from the first part of the cigarette. Women smoke more filter-tip cigarettes than men, and smoke more "low tar and nicotine" cigarettes than do men. They also inhale less frequently and deeply than men. Furthermore, cigarette smoking still tends to be heavily concentrated in those women under the age of 50 years, prior to the age at which lung cancer is mostly likely to occur.

An anlysis of the lung cancer death rates (*94*) shows that, "Until 1960 the ratio of the death rate in the male population for this cause to the corresponding death rate in the female population continued upward. But after 1960 this ratio leveled off, reflecting the greater relative rise in mortality from lung cancer in the female population."

Additional Considerations and Conclusions

Filter cigarettes, in general, have lower "tar" and nicotine values than comparable non-filter cigarettes. In this respect, a study by Bross (*9*), shows preliminary evidence that smokers who switched to filter cigarettes have a decreased risk of developing lung cancer.

Graham (*30*) studied the smoking habits of male lung cancer patients and controls. Previously he showed, on smoking machines, that dif-

ferent patterns of cigarette smoking gave different "tar" yields. His lung cancer patients had significantly greater high "tar" yield cigarette smoking patterns than the controls. The risk of lung cancer increased with increase in: (1) the mean number of puffs per cigarette, (2) the average length of time taken to smoke a cigarette (except in the highest number of puffs category) and (3) taking more puffs towards the end of the cigarette. These findings add further support to the dose-response relationship between lung cancer and cigarette "tar" exposure.

As pointed out in the 1964 and 1967 Reports, there appear to be several other factors which may also contribute to the etiology of lung cancer, especially in the presence of cigarette smoking. However, there has been no evidence to refute the statement in the 1964 Report that, "Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction."

Of particular interest are the studies of Buell, et al. (*11*, *12*). They reviewed various prospective and retrospective studies which showed that the urban-rural differences in lung cancer death rates in non-smokers were of the range of 2 : 1 to 4.4 : 1. However, the much greater effect of smoking on increasing the lung cancer death rates was evident by their statement "that smoking can act independently of the urban factor, the gradients among rural dwellers rising to as much as 10 to 15 fold for heavy smokers." With regard to the high levels of photochemical air pollutants in Los Angeles, they concluded: "With controls for cigarette smoking and length of residence, the risk of pulmonary cancer in Los Angeles, where photochemical air pollution levels are highest, was not greater than in other major metropolitan areas of California."

Although photochemical air pollution might not be a contributing factor to lung cancer mortality in man, as is the "sulfur dioxide" air pollution found in most industrial areas, it may be too early to ascertain any effects, since air pollution in Los Angeles only became a problem between 1945 and 1950.

Stocks (*84*, *85*) shows that per capita solid fuel consumption has a positive correlation with lung cancer death rates but to a much lesser degree than per capita cigarette consumption. He suggests, therefore, that air pollution from solid fuel combustion is related to lung cancer death rates and that this might possibly be independent of cigarette smoking. However, Stocks did not determine the specific smoking histories of individuals who died from lung cancer.

Concurrent studies of cigarette smoking and air pollution, in the same populations with precise smoking histories on individuals who have died from lung cancer, might serve to clarify the probable interaction between cigarette smoking and air pollution or possible inde-

pendence of cigarette smoking from air pollution as they relate to the etiology of lung cancer.

The preponderance of evidence [1964 Report (*91*), 1967 Report (*92*), and this report] continues to indicate that most lung cancers occur in cigarette smokers and that cigarette smoking is the major cause of lung cancer. A majority of lung cancer cases are of the squamous cell variety and most investigators are in agreement that squamous cell carcinoma is rare in the male nonsmoker (*3*, *15*, *103*). The elimination of cigarette smoking would in time eliminate most lung cancer. That this is a real goal is supported by the study of British physicians (*18*, *19*) reviewed in the 1967 report.

It is not disputed that some cases of lung cancer can occur in those people who have never smoked cigarettes or inhaled any form of tobacco smoke. In these cases air pollution possibly plays a larger role in the causation, but in most cases, it appears that it is the cigarette smoker who is especially susceptible to whatever additional risk for lung cancer may be presented by certain types of air pollution or other factors such as asbestos or uranium dust inhalation.

CANCER OF THE ORAL CAVITY

The 1967 report showed that the overall death rates for oral cancer remained about the same during the period 1950–1964. This was influenced somewhat by recent changes in the ICD Code.

It is interesting to note that the incidence rates of oral cancer have also remained relatively constant over the period 1935–1962,* in spite of increased cigarette smoking (*24*). This may be explained, in part, by the fact that the numerators of such rates often include neoplasms coded to the International Classification of Disease, rubrics 140 through 148. These rubrics identify many oral and pharyngeal diagnostic sites which do not contribute equally to either the morbidity or mortality experience resulting from the use of tobacco. For example, preliminary findings in an unpublished study by Keller (*47*) suggest that salivary cancers (ICD rubric 142), unlike tongue and floor of mouth cancers, are not associated with the tobacco habit. The fact that pipe and cigar smoking in this country began to be replaced by cigarette smoking among men born subsequent to 1900 may also be significant, although this trend has leveled off and may even have been reversed since the health consequences of smoking cigarettes first came to public attention in the mid-1950's. In the population which accounts

*There is no national data collection on incidence rates of diseases. Several states have cancer registries which have information on the incidence of cancer in that particular state. The data from Connecticut are generally thought to reflect the changing patterns of cancer incidence throughout the United States. It is realized that there might be individual state differences. References to incidence rates in this chapter section are taken from the Connecticut data unless otherwise specified.

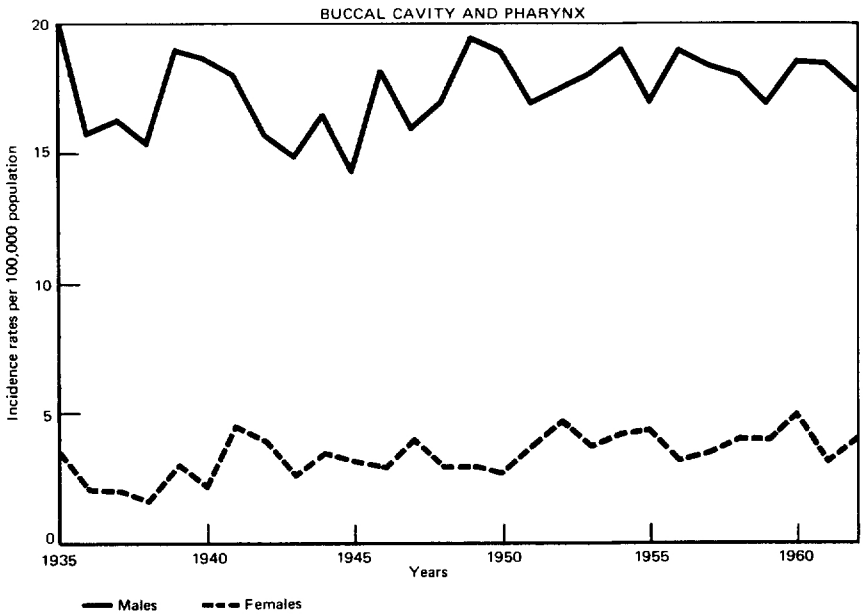

FIGURE 2—Age-adjusted rates of the incidence of cancer of the buccal cavity and pharynx, for males and females: Connecticut, 1935–1962.

SOURCE: Eisenberg, et al. (*24*).

for the bulk of oral cancer cases—men over 45—there has been a greater change in the form in which tobacco is used than in the proportion of men using tobacco.

Since pipe and cigar smoking is associated with oral cancer, with mortality ratios not very different from those for cigarette smokers, the constant incidence rates may reflect the fact that the proportion of tobacco users among men over 45 has been fairly stable.

A review of the recent retrospective studies shows a relationship of oral cancer to all forms of the tobacco habit (*22, 26, 53, 54, 77, 78, 79, 98*). This includes the use, in the mucobuccal fold, of either snuff, among women (*10, 22, 71, 72, 81*), or the betel nut quid with tobacco, among the residents of India and Southeast Asia (*36, 54, 77, 78, 79, 98*).

Reddy has produced tumors in mice by daily instillation of a "pan" mixture with tobacco (the same mixture used for chewing) into the vaginas of virgin mice (*69*).

There is evidence that in the presence of tobacco consumption, alcohol may also be a factor in the etiology of oral cancer (*48, 49, 50, 97*). In a recent study on male veterans, Keller concluded, "* * * heavy smoking, heavy drinking and liver cirrhosis (either alone or as a measure of heavy drinking) are associated with cancer of the