SMOKING AND LUNG CANCER
A STATEMENT OF THE PUBLIC HEALTH SERVICE
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The Public Health Service is deeply concerned with the increasing death rate from lung cancer in the United States and in other parts of the world. Cancer of the lung is increasing more rapidly and causing more deaths than any other form of cancer in the adult male population. In the United States, the death rate from lung cancer among white men (age-adjusted) was 3.8 per 100,000 population in 1930; by 1956, the rate had risen to 31.0, and more than 29,000 persons died of lung cancer in that year (fig. 1, table 1). A rising death rate of this magnitude arrests the attention of every physician, private practitioner and public health officer alike.

Many investigators have indicted cigarette smoking as responsible in large part for the increasing lung cancer death rate. Others have denied this, saying that increased volumes of automobile exhaust fumes and industrial vapors polluting the air are largely responsible for the causation of lung cancer. The possibility that there are other factors yet unknown has also been suggested.

Two years ago I made the following statement: "The Public Health Service feels the weight of the evidence is increasingly pointing in one direction: that excessive smoking is one of the causative factors in lung cancer." Our belief then was based on reports that had been accumulating for more than 20 years. Since 1957, additional studies, some from our own staff, have contributed new information. I wish, in this paper, to review the data in those publications the Public Health Service has felt to be of particular value and to give our interpretation of the material presented.

The Smoking Hypothesis
In their classic study in 1928, Lombard and Snegireff noted an association between heavy smoking and buccal cancer. Later, examination of time trends in mortality showed that the death rate from lung cancer was rapidly increasing. This immediately raised the question of a possible association of smoking with bronchial malignancy. Many studies in different countries showed a higher proportion of smokers in lung cancer groups than in control groups.

Lombard and Snegireff. The latest paper in the Massachusetts studies on lung cancer and smoking deserves particular mention. The documenting of each case is unusually thorough, covering a wide range of factors. An extensive series of controls was subjected to the same scrutiny. In a series of patients known to have died of lung cancer, four variables showed significant correlation and association: frequent or chronic respiratory conditions, heavy cigarette smoking, heavy consumption of alcohol, and outdoor work. Of these four variables, heavy cigarette smoking had by far the strongest relationship to lung cancer. "About four-fifths of the persons with lung cancer were heavy cigarette smokers (more than 9,125 packages), . . . about one-third had frequent or chronic respiratory conditions, one-fifth were engaged in outdoor occupations, and about one-seventh were users of alcohol in excessive amounts."

However, there was criticism of the retrospective (historical) method, on which this paper and the earlier ones were based, as being subject to unavoidable bias. The following three studies, recently published, were designed therefore with a prospective (continuing) approach. Doll and Hill reported from England, Hammond and Horn for the American Cancer Society, and Dorn from the National Cancer Institute of the Public Health Service (fig. 2 and 3). Doll and Hill-The Doll and Hill study is a continuing analysis of 40,701 British physicians. Among male physicians 35 years of age and over, in the initial four and one-half years of observation, 1,714 deaths have occurred, including 84 from lung cancer. Deaths from lung cancer increased steadily with increasing amounts smoked; for non-smokers (age-adjusted) death rate was 7 per 100,000 of this population; for light smokers, 47; for moderate smokers, 86; and for heavy smokers (more than 25 cigarettes daily), 166. Giving up smoking reduced the susceptibility of a smoker to subsequent development of lung cancer. The decrease was greatest in those who had given up the habit for a decade or more. Those who continued to smoke more than 25 cigarettes daily from the beginning of the study had a mortality from lung

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cancer nearly 40 times that of the nonsmokers. Pipe smoking was associated with lung cancer to a lesser degree than was cigarette smoking.

Hammond and Horn—Hammond and Horn have been conducting a longitudinal study of 187,783 white men aged 50 to 69. Analyses with regard to lung cancer in this age group at the end of 44 months support the findings of Doll and Hill. The 82,932 men who never smoked had an age-adjusted death rate from all types of lung cancer of 12.8 per 100,000 man-years. On the other hand the 63,332 men who gave a history of smoking cigarettes exclusively showed an age-adjusted death rate from this cancer of 127.2, a ratio of 10 to 1.

This study of Hammond and Horn is of particular interest since the reports of the individual deaths due to lung cancer were carefully checked and in most cases verified by microscopic diagnosis. The tumor deaths proved by tissue section constituted what the authors called the "well-established cases," on which further detailed studies were made. Adenocarcinoma of the lung was excluded from this group and treated separately because of the small number of cases (32) and also because of the general feeling that adenocarcinoma may be less associated with smoking than are other forms. Table 2 summarizes much of the Hammond and Horn study.

Within the group of "well-established cases" the difference in death rates between the nonsmoker and the heavy smoker was striking, the ratio being 64 to 1. For those who had previously smoked cigarettes but had stopped the death rate was significantly reduced, and, as the period without smoking lengthened, the death rate became progressively lower, although it never reached the rate of those who had never smoked (fig. 3).

Dorn.—The Dorn study population consisted of 249,000 U. S. government life insurance policy holders. At the end of two and one-half years of this continuing study there had been 7,382 deaths in the group. The increased proportion of deaths from any cause among the smokers as compared with the nonsmokers was greatest for cancer of the lung. The death rate from this malignancy among regular smokers of cigarettes was about 10 times that in the nonsmoking group. Regular cigarette smokers who had stopped smoking cigarettes before the study began in 1954 had a lower mortality than those who continued to smoke; however, this rate was still 30% greater than for nonsmokers.

**Fig. 2.—Number of deaths from lung cancer in smokers for each death in nonsmokers, by study.**

**Criticism of the Smoking Hypothesis.**—Not all investigators are in agreement with the conclusions reached by these researchers.

Berkson noted that the data of Hammond and Horn and of Doll and Hill point not only to an association between smoking and lung cancer but also to a wide variety of diseases never presumed to have the same etiology as cancer. He suggests that some other explanation must be sought, stating, "1. The observed associations are 'spurious, that is, they have no biological significance, but are the result of the interplay of various subtle and complicated biases.' The definitive variables, namely a history of smoking and the cause of death, are, as observations, subject to considerable error, and the samples, not having been obtained (or obtainable) by scientific sampling methods, are 'selected.'..."

"2. The observed associations have a constitutional basis. Persons who are nonsmokers, or relatively light smokers, are the kind of people who..."
are biologically self-protective, and biologically this is correlated with robustness in meeting mortal stress from disease generally.

"3. Smoking increases the 'rate of living' (Pearl), and smokers at a given age are, biologically, at an age older than their chronologic age. As a result, smokers (in particular, heavy smokers) are subject to the death rate of nonsmokers or relatively light smokers who are chronologically older. . . ."

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selves encourage a desire to smoke.” There may be secondary agents responsible in the “final efflorescence” of the disease in later years.

Herdan, also in England, noted that death rates from tuberculosis and lung cancer seem bound together as a constant. As one has gone down the

Table 2.—Number of Deaths and Age-Standardised Death Rates from Lung Cancer by Smoking Habits

<table>
<thead>
<tr>
<th>Smoking Habits</th>
<th>All Cases</th>
<th>Well-Established Cases (Excluding Adenocarcinomas)</th>
<th>Adenocarcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Rate</td>
<td>No. Rate</td>
<td>No. Rate</td>
</tr>
<tr>
<td>Never smoked</td>
<td>13 12.8</td>
<td>4 2.4</td>
<td>2 1.8</td>
</tr>
<tr>
<td>Cigars only</td>
<td>8 19.2</td>
<td>5 11.9</td>
<td>1 2.3</td>
</tr>
<tr>
<td>Pipes only</td>
<td>7 13.1</td>
<td>6 11.4</td>
<td>1 1.7</td>
</tr>
<tr>
<td>Cigars and pipes</td>
<td>3 7.3</td>
<td>2 4.9</td>
<td>0 ...</td>
</tr>
<tr>
<td>Cigarettes and other</td>
<td>14 17.7</td>
<td>2 4.9</td>
<td>0 ...</td>
</tr>
<tr>
<td>Cigarettes only</td>
<td>4 17.7</td>
<td>2 4.9</td>
<td>0 ...</td>
</tr>
<tr>
<td>Total</td>
<td>41 68.9</td>
<td>28 46.6</td>
<td>20 31.7</td>
</tr>
</tbody>
</table>

* Death rate per 100,000 man-years standardised to the age distribution of the white male population of the United States as of July, 1954.
† Data from Hammond and Horn.

other has risen, so that the “probability that a person should die of either respiratory tuberculosis or C.L. [cancer of the lung] remains sensibly constant in the population.” He believes that it is the antibiotic therapy of tuberculosis “resulting in the reduction of the combined mortality of males and females due to pneumonia and tuberculosis of the lung, which is responsible for bringing to the fore a disease which has its roots, partly at least, in the genetic make-up of man.”

Supporting Opinions.—On the other hand, two groups of equally prominent authorities have come to an opposite conclusion. In June, 1956, the American Cancer Society, the American Heart Association, the National Cancer Institute, and the National Heart Institute, by joint action, organized the Study Group on Smoking and Health to review the effects of tobacco smoking on health and to recommend further needed research. After six two-day conferences, exhaustive examination of the literature, and discussion with scientists representing specialized areas of research concerned with the subject, the Study Group made this official statement: “The sum total of scientific evidence establishes beyond reasonable doubt that cigarette smoking is a causative factor in the rapidly increasing incidence of human epidermoid carcinoma of the lung.”

The second group, the British Medical Research Council, in 1957 published the following conclusions. “A very great increase has occurred dur-

ing the past 25 years in the death rate from lung cancer in Great Britain and other countries. 2. A relatively small number of the total cases can be attributed to specific industrial hazards. 3. A proportion of cases, the exact extent of which cannot yet be defined, may be due to atmospheric pollution. 4. Evidence from many investigations in different countries indicates that a major part of the increase is associated with tobacco smoking, particularly in the form of cigarettes. In the opinion of the Council, the most reasonable interpretation of this evidence is that the relationship is one of direct cause and effect. 5. The identification of several carcinogenic substances in tobacco smoke provides a rational basis for such a causal relationship.”

Other Factors

Since carcinoma of the lung is a disease that also occurs in nonsmokers, it is evident that factors other than tobacco contribute to its etiology. The major exogenous factors are air pollution and occupational exposure to carcinogens. The latter accounts for only a small percentage of lung cancer deaths.

Air Pollution.—Air pollution may be the “urban factor” which would help explain the higher death rate from lung cancer in urban as compared with rural areas (fig. 4). The major sources of air pollution are exhaust products of gasoline and diesel engines, incomplete combustion products of petroleum and coal, many asphalt and bituminous products used in construction and road paving, and certain industrial effluents. The carcinogenic sub-

Fig. 4.—Age-adjusted lung cancer death rates for cigarette smokers and nonsmokers—urban-rural comparison (based on data from Hammond and Horn).
environmental factors contributing to the rise in lung cancer (fig. 5). There are also noncarcinogenic pollutants which are irritants and may affect the body's defense mechanism against inhaled carcinogens.

Socioeconomic Status.—Some investigators have found that low socioeconomic groups have an increased incidence of lung cancer. However, the low income group, by economic necessity, is apt to live near industrial centers where the air is more heavily contaminated with pollutants and airborne carcinogens than it is in peripheral residential areas. It is also true that the low socioeconomic group, as a whole, receives less adequate medical care and lives in a less hygienic environment than the more fortunate portion of society. Thus, it is difficult to measure any direct effect of socioeconomic factors alone.

Lower Mortality in Women.—Until 1926 lung cancer death rates among men and women in Massachusetts (and, presumably, in the rest of the United States), were approximately equal. As lung cancer rapidly increased, its distribution between the sexes changed. In 1956, in both Massachusetts and the United States, the mortality in men was more than five times that in women. This difference is not easily explained. There may be a true sex difference in susceptibility to the causes of increase in lung cancer, but the data are not conclusive.

Studies of apparent differences in smoking habits also have not accounted adequately for the variation in death rates between men and women. But there is conclusive evidence that nonsmoking women have about the same lung cancer death rate as nonsmoking men; that among women, the light smoker carries a risk of lung cancer twice that of the nonsmoker; and for the woman smoking more than one pack a day, the hazard is five times greater.

Physical Factors—Pipe and Cigar Smoking.—Hammond and Horn have shown that a person who smokes cigarettes has almost three times the risk of dying from lung cancer as the pipe smoker

(fig. 6) and seven times that of the cigar smoker. It is possible that this relatively favorable status of pipe or cigar smokers may be due to the more adverse physical characteristics of cigarette smoke. Cigarettes burn at considerably higher temperatures than pipes or cigars. Undoubtedly, too, deep inhalation of smoke is associated almost entirely with cigarette smoking. Others maintain that the lower death rates of persons who do not smoke cigarettes exclusively merely reflect their less extensive use of cigarettes.

A Concept of Pathogenesis of Lung Cancer

The association between the use of tobacco and buccal and lung cancer has been supported largely by statistical evidence until relatively recently. This in itself has seemed conclusive to many investigators, although the mechanism of cancer growth in the lung has never been demonstrated. If the smoking hypothesis is valid, it should be possible to show a sequence of events, started by cigarette smoke, which leads to the development of lung cancer. The same course could be initiated by the inhalation of carcinogens from polluted air. Several recent investigations lend support to such a concept of pathogenesis. It should be noted that this concept is theoretical, for the full course from causative agent to final tumor is not known in man. Furthermore, the statistical and experimental association between smoking and lung cancer applies essentially to the epidermoid type. The incidence of adenocarcinoma and undifferentiated carcinoma of the lung has changed little.

Carcinogenic Substances.—It has long been known that certain polycyclic hydrocarbons are carcinogenic for animals and man. Those present in the tobacco leaf are fragmented at the burning temperature of the cigarette into incomplete combustion products and are included in the tar portion of the smoke. Wynder has shown that cigarette
tar produces cutaneous papillomas and carcinomas when applied for prolonged periods to the skins of laboratory animals. Confirmation of these studies has been reported from other laboratories. There is little doubt that benzpyrene and other carcinogenic hydrocarbons found in soot are responsible for the classic human example of occupational cancer, Pott's epidermoid carcinoma of the serotum in chimney sweeps. Cooper in 1955 first demonstrated the presence of 3,4 benzpyrene in cigarette smoke. Benzpyrene is probably not the only carcinogen involved.

Absorption by Cells.—Mellors demonstrated that cells can absorb carcinogenic substances. When he gently scraped human squamous epithelial cells from the buccal mucosa and placed them in millionfold dilutions of cigarette tars, these same cells became "stained" by the products of cigarette tars and fluoresced characteristically when examined with the fluorescent microscope.

The Flow of Mucus and Ciliary Action.—Robertson has reported on the phagoctytic action of histiocytes extruded into the lumen of the alveolus. Macklin noted that the alveolus is the point at which inhaled smoke comes into intimate contact with the rich capillary bed of the lung. The phagocytes appear to move out of the alveoli, along with a thin, mucoid coating, until the ciliated areas of the sub-bronchioles are reached. By the propelling force of ciliary action the mucous blanket, laden with foreign particles such as insoluble tobacco tars, moves slowly toward the trachea. From the relatively great total area of the alveolar regions the mucous stream follows a steadily narrowing path to the hilar regions where, by comparison, the cross-sectional area of the large bronchi is very small. During this passage the mucous blanket apparently becomes thickened and less fluid. Thus, the mucus is funneled and concentrated, along with its adherent tars, into the hilar areas, where there are additional mechanical reasons for stasis.

Concentration.—Occurring normally in the hilar bronchi are the numerous apertures of emerging bronchioles and patchy islands of nonciliated epithelium. Hilding produced deciliated areas by injuring the bronchial mucosa and showed that the flow of the mucous blanket hesitates at these deciliated areas. In his study of the bronchi of freshly killed calves both India ink and, again, smoke were introduced into the mucous stream and observed for varying periods. When foreign material struck either the normally nonciliated regions or the areas of injured cilia, the particles collected on the "upstream" side and lagged behind, remaining in contact with the bronchial epithelium for prolonged periods before being swept on. There is no report as yet of a similar study in man.

Autopsy Studies.—Auerbach and co-workers reasoned that lungs of smokers should reveal both destructive lesions and precursors of malignant change in the epithelium of the tracheobronchial tree. Their conclusions are based on some 25,000 sections from autopsies of 117 patients in whom the authors found changes they described as basal cell hyperplasia, stratification, squamous metaplasia, and carcinoma in situ. The cellular changes showed a statistically significant, increasing gradation. Sixteen nonsmokers had the fewest abnormalities. A higher percentage of abnormal slides were noted in the 20 patients who had smoked less than one package of cigarettes a day. Still more atypical were the findings in 47 patients who had smoked more than one package a day. Thirty-four patients dying of bronchial cancer (all smokers) showed the greatest number of areas of cellular aberration.

The Concept of Pathogenesis.—Tars containing benzpyrene and probably other carcinogens present in cigarette smoke (or contaminated air) are absorbed by the cells of the respiratory tract, especially in the alveoli. Here these foreign particles are picked up by phagocytes and transported toward the trachea in the mucous blanket of the bronchi. On route, concentration occurs where the cilia of the bronchial mucosa are injured or absent, and the motion of the mucous blanket is stopped for appreciable lengths of time. During this period the carcinogens contained in "tar" particles and in the mucus are afforded prolonged contact with the underlying bronchial cells, which react by malignant change.

Experimental Proof.—Experimental proof of this concept, to date, has not been supplied. The ultimate experiment would produce in laboratory animals, by the same type of exposure that occurs in humans, the same type of terminal tumor, preferably through the same sequence of preliminary changes as has been postulated above.

Rockey and his associates applied tobacco "tar" directly to the bronchial mucosa of dogs and found that within three to six weeks the tar-treated surfaces became granular and later developed wart-like elevations. In the study of Leuchtenberger and co-workers mice were exposed to cigarette smoke and examined after varying periods, the longest being 200 days. In most animals the bronchial epithelium showed inflammation and simple and atypical basal cell hyperplasia. Passey stated, however, "Our failure during the past five years [recorded in previous publications] to induce lung tumours in mice, rats, and hamsters by exposure to strong concentrations of cigarette smoke is a striking negative result."

The findings of such experiments, in toto, are inconclusive. Whether this is due to inherent difficulties of the experimental methods employed or to the problem of adequate control, or whether this represents a true negative is not apparent at present.
Future Possibilities for Prevention

There can be no doubt that a significant proportion of the increase in lung cancer is real. This rise has not been caused solely by improvements in diagnostic techniques, better reporting on death certificates, or an increase of older persons in the population. If we accept as valid the sequence of pathological changes given above, the prevention of lung cancer, to a large extent, becomes possible. This will be accomplished if carcinogenic substances from any source can be kept out of the air inhaled into the lungs.

Use of Filter Tips.—Filter tip cigarettes, which accounted for 1.4% of the market in 1952, now constitute approximately 50%. This suggests that both the public and the manufacturers are concerned that some avoidable toxic agent may be contained in the tobacco smoke. Because the public has widely accepted filtered cigarettes, it is necessary to examine the effectiveness of the filtration.

Present knowledge indicates that it is not possible to filter, selectively, specific components such as carcinogens. Since the evidence from both human and animal studies shows that the risk of developing cancers is related to the amount of exposure to tar, the problem is to design a filter that will permit the minimum flow of whole tobacco smoke to pass, consistent with smoking satisfaction. The filters presently in use do not eliminate, but merely reduce, the tar. It is questionable whether, from a health point of view, any so-called minimum exposure to such a hazard should be accepted.

Table 3 gives the status of filters today, as found in two recent independent studies. In both studies cigarettes were smoked to a standard butt length, at a standard rate, volume, and duration of puff. Any reduction in tar content of the smoke is accomplished only if the consumer does not smoke more than formerly and if the manufacturers do not alter the tobacco selection, cut, or packing to counteract any deficiency in taste caused by the filter.

It has been shown also that, whereas the major portion of carcinogenic substances is present in the tar, others may be found in the paper of the cigarette or in the tobacco additives used.

Tobacco Treatment.—The possibility exists, in theory at least, of treating the tobacco before it is packed into cigarettes so as to eliminate the hazard of cancer. In practice, however, this has not been demonstrated.

Air Filtration.—Most investigators agree that air pollutants probably contribute to the elevated lung cancer death rate. Cancer-producing agents are in the air we breathe. Cancer can be produced in animals, with use of concentrates of urban smog. The cancer death rate in the largest cities is twice as high as that in nonurban areas. The case is not yet proved, but the weight of evidence grows heavier as research progresses.

It should be possible to reduce the amount of noxious material being discharged into the atmosphere by industry and by internal combustion engines. Most of the major cities in this country have well-established smoke-control programs. Industry has done much already to institute better methods of combustion in manufacturing processes and to develop means of extracting pollutants from smoke and vapors before they are discharged into the air. Automobile makers now have devices in the laboratory stage that show promise of controlling the exhaust pollutants produced by the new fuels and the modern high-compression automobile engine. Further study and effort are required, but marked reduction in the future of carcinogenic air contamination is technically and practically feasible.

Change in Smoking.—Approximately 60% of the men and 30% of the women in the United States over 18 years of age smoke cigarettes. Slightly higher incidences are found in the United Kingdom.

Recently two persons on the staff of the Public Health Service contributed to a review of the important studies in this field, including, among other papers, those listed above as critical of the smoking hypothesis. The group of statisticians and epidemiologists reporting this study recognized that "there are areas where more research is necessary" and that "no single cause accounts for all lung cancer." However, they concluded that "the magnitude of the excess lung cancer risk among cigarette smokers is so great that the results cannot be interpreted as arising from an indirect association of cigarette smoking with some other agent or characteristic." If cigarette smoke carries carcinogens, control of smoking, no matter how difficult it may be, becomes a major factor in prevention of bronchial carcinoma.

Conclusions

It is a statutory responsibility of the Public Health Service to inform members of the medical profession and the public on all matters relating to important public health issues. The relationship between smoking and lung cancer constitutes such an issue and falls within this responsibility of the Public Health Service.

The Public Health Service believes that the following statements are justified by studies to date.

1. The weight of evidence at present implicates smoking as the principal etiological factor in the increased incidence of lung cancer.
2. Cigarette
smoking particularly is associated with an increased chance of developing lung cancer. 3. Stopping cigarette smoking even after long exposure is beneficial. 4. No method of treating tobacco or filtering the smoke has been demonstrated to be effective in materially reducing or eliminating the hazard of lung cancer. 5. The nonsmoker has a lower incidence of lung cancer than the smoker in all controlled studies, whether analyzed in terms of rural areas, urban regions, industrial occupations, or sex.

6. Persons who have never smoked at all (cigarettes, cigars, or pipe) have the best chance of escaping lung cancer. 7. Unless the use of tobacco can be made safe, the individual person's risk of lung cancer can best be reduced by the elimination of smoking.

References


26. (a) Krejberg, L.: Significance of Histological Typing in Study of Epidemiology of Primary Epithelial Lung Tumors: Study of 466 Cases, Brit. J. Cancer 8:199-208 (June) 1954. (b) Hammond and Horn.\(^8\)


48. (a) Doll and Hill.\(^7\) (b) Hammond and Horn.\(^8\) (c) Dorn.\(^8\)

49. (a) Doll and Hill.\(^7\) (b) Hammond and Horn.\(^8\)