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## **Lung Cancer and Smoking: What We Really Know**

The American Cancer Society has already spent more than half a million dollars on its research on lung cancer, and the Board of Directors recently authorized a second half-million dollars with which to carry forward the investigations. In the article which follows, Dr. Charles S. Cameron, Medical and Scientific Director of the Society, summarizes the important evidence thus far and gives an answer to those who still deny that an association between smoking and lung cancer does exist.

During the last two years, a lot has been written—and said—about the dangers of cigarette smoking, especially as a possible cause of the alarming increase in cancer of the lung. But there is still much confusion about the tobacco-cancer issue. Most of the scientists who have given thought and study to the matter appear to agree that an association between cigarette smoking and cancer of the lung does exist. Whether that association is one of cause and effect is as yet unanswered in terms of major scientific opinion.

One of my colleagues expresses the situation in this way: If it has not been proved that tobacco is guilty of causing cancer of the lung, it has certainly been shown to have been on the scene of the crime. The American Cancer Society, along with a growing body of professional and scientific opinion, has taken this position: Although the complicity of the cigarette in the present prevalence of cancer of the lung has not been proved to the satisfaction of everyone, yet the weight of evidence against it is so serious as to demand of stewards of the public welfare that they make the evidence known to all.

Most authorities on the subject agree that before the early years of the twentieth century, cancer of the lung was encountered rarely. In a monograph on lung cancer which was notable in its day—1912—Adler could base his review on a mere 374 cases. Today cancer of the lung takes the lives of about as many white males each year as were reported to have died of all forms of cancer combined in 1900. During the period 1930-1948, the death rate from lung cancer among men rose from 5.3 per 100,000 to 27.1—an increase of 411 per cent. Some part of this remarkable increase can be laid to better and more widely available diagnosis, but the net impact of the factor of better diagnosis is considerably weakened by noting the trends in the post-mortem experience in large hospitals over the years. Cancer of the lung was perhaps less generally recognizable forty or fifty years ago than it is today—but that was hardly true in the autopsy room. Cancer of the lung now constitutes a substantially larger proportion of the total autopsy findings than it did thirty years ago.

There are certain curious features of this increase. In the first place, whereas the curve of the death rate from nearly every type of cancer affecting chiefly adults rises steadily with increasing age, that for cancer of the lung does not. As early as 1936 the rates by age for white males showed a flattened peak between the ages of 60 and 75, after which it fell off. The peak has since become high and sharp, and for the years 1945-1948 occurs at about the ages 65 to 70, after which the rates drop abruptly. The rate curves for women show later peak death rates, tending to resemble more closely the curves for other types of cancer. The only reasonable explanation for this phenomenon is as follows: From what is known about established environmental causes of human cancer, those causes appear to require years of operation, usually not less than twenty, but sometimes longer, in order to exert their effect. The lung cancer death rate curve suggests that whatever agent (or agents) is responsible for the present increase in cancer of the lung is of recent appearance in terms of its current prevalence, did not involve men who are now beyond the age of 70, but did involve men who are 65 to 70, and in the light of the usual exposure period necessary to produce cancer, about twenty to thirty years ago. This puts the critical exposure period in the 1920s and early 1930s, when the present susceptibles were relatively young men.

The second unique feature of lung cancer death rates over the years is the growing disparity between the sexes. In the period 1933-1936, the ratio was slightly over two male deaths to one female death from this disease. In the interval 1945-1948, five men died from lung cancer for every woman dying from the same cause. In 1949 the difference had increased to six to one, and today most opinions put the male-female ratio of deaths at eight or nine to one. It would appear that more men than women have exposed themselves to whatever factors are responsible for the recent rise of this disease.

Thirdly, cancer of the lung is commoner by a factor of more than 2 among white males living in cities than it is among country dwellers. The differences are much less marked for women, but are nonetheless discernible.

Now, why is this so? Suspicion falls first on substances which are inhaled, because almost all of the 400-odd cancer-producing substances discovered since Yamigawa provided the first demonstration of experimental cancer causation in 1915 exert their effect at the site of contact. What are we inhaling which is widespread, which is more prevalent in cities, which is recent, which is increasing, and to which more men than women are, or rather have been, exposed?

Prominent on the suspect list are industrial fumes; utility, industrial, and domestic soots derived from coal and fuel oil furnaces; exhausts from internal combustion engines (gasoline and diesel), asphalt or bituminous road surfaces; and cigarette smoke.

Industrial fumes have increased, of course; yet, because there is no satisfactory index for the amount of increase and because of their heterogeneous nature, it is most difficult to establish their relationship to the general increase of lung cancer. Coal consumption has not increased in the United States over a period of many years; therefore coal soot would not seem to be an important factor. But fuel oil sales have increased greatly, the volume of annual consumption now being about three and one-half times greater than it was thirty years ago.

Particulate and fume exhausts from motor vehicles contribute heavily to air pollution, and the magnitude of their increase may be roughly gauged by the number of motor vehicles currently registered in the United States as compared with the figure of thirty years ago (three times greater) and by the rate of yearly motor fuel consumption now as compared with 1933 (five times greater).

Roads surfaced with asphalt and oils—bituminous products belonging to the polynuclear hydrocarbon family of chemical compounds—have been cited as sources of fine dusts which on the theoretical grounds of chemical derivation may be cancer inciters. And there is laboratory evidence which renders motor vehicle exhausts and the general atmosphere of at least one large city suspect.

As to tobacco, for most of its long history it was employed almost exclusively in the form of pipe or cigar smoking, with snuff enjoying wide use during the reign of Victoria. It is significant that cigarettes did not begin to achieve popularity until after the turn of the present century—a fact attributed to two innovations: 1) mixture improvements making for better burning quality, and 2) mass production by machines. In the twenties, cigarettes took the inside track, and by 1935 were exceeding all other forms of tobacco use (including chewing) as measured by pounds consumed per capita. Last year in the United States 10.5 pounds of tobacco per capita were consumed as cigarettes, as against 1.25 pounds per capita as cigars and 1.19 pounds per capita in the form of pipe and chewing tobacco and snuff. Expressed another way, during the past thirty-three years there has been a 456 per cent increase in the volume of cigarettes consumed per person in the United States.

## 2.

While a number of observations leading to the same conclusion had appeared prior to 1928, properly controlled statistical studies of a possible relationship between cigarette smoking and lung cancer may be said to have begun with the investigation by Drs. Herbert Lombard and Carl Doering of the State Department of Health of Massachusetts, the conclusion of which, published in that year, was that heavy smoking appeared a good deal more often in the histories of patients with cancer than it did among those of comparable ages without cancer. Ten years later Raymond Pearl published the results of his extensive study of the effect of smoking on length of life. They may be summarized this way: Of a given number of men alive at the age of 30, 66.6 per cent of the non-smokers will be living at age 60 as compared with 46.2 per cent of heavy smokers; at age 75, 33.8 per cent of nonsmokers and 22.3 per cent of heavy smokers will be living. After 75, the differences become insignificant, indicating that there are some people so impervious to noxious influences as to remain highly durable in spite of them. In 1945, a further report of the study of smoking and career by the

State Department of Health of Massachusetts disclosed a decided association between the use of tobacco and the incidence of cancer of the mouth and lung.

The year 1950 saw the publication of four independent statistical studies, each of which established a significantly higher percentage of heavy cigarette smokers among lung cancer patients than among any other group. There have now been more than fourteen similar studies, and without exception they arrive at this same conclusion.

But there are intrinsic weaknesses in the design of retrospective studies of this kind—weaknesses which made many, including ourselves, skeptical of the results. And it was our own disbelief which led to a comprehensive statistical investigation of the prospective type.

Under the guidance of the American Cancer Society's Advisory Committee on Statistics—a group of statistical experts of acknowledged experience and competence—Drs. E. C. Hammond and Daniel Horn devised an investigation scheme in which the smoking histories of a very large number of men not known to have cancer of the lung were recorded. Histories were obtained from over 187,000 men between the ages of 50 and 70. They included men who had never smoked, those who had smoked exclusively either cigarettes or pipes or cigars, and those who had indulged in mixed smoking practices. The approximate quantities smoked were also set down. After 18 months, the first follow-up analysis was begun and it was found that 4854 deaths had occurred in the study group.

First, it became apparent that the death rates among the men with some history of regular cigarette smoking were one and one-half times greater than the number among the non-smokers. The cancer death rate (regardless of the kind of cancer) was two and one-half times greater in heavy cigarette smokers—a pack or more a day—than in the non-smoking group. Heavy cigarette smokers died of heart disease at nearly twice the rate of those who had never smoked. The death rates from cancer of the lung were at least five times higher in the heavy cigarette smoking group than in nonsmokers. Death rates were appreciably higher among men who smoked cigarettes lightly (less than one-half pack a day) than among nonsmokers. In general, death rates among regular smokers of pipes and cigars were somewhat higher than among those who had never smoked, but not so high as among the cigarette smokers.

The study also revealed that a higher percentage of men in rural districts had never smoked and a lower percentage had a history of regular cigarette smoking than was found in urban centers.

These first returns confirmed the conclusions of the previous studies based on altogether different fact-gathering methodology. And since its publication, a somewhat smaller investigation using essentially the same technique with 60,000 British physicians as subjects has reported practically identical results.

### 3.

It is tempting to make a variety of calculations based on these and other data bearing on lung cancer incidence, but I shall confine myself to those which I believe are the most meaningful. Based on the assumption that present mortality rates for lung cancer will continue and that present over-all death rates will continue, the chance of a young adult male's developing lung cancer is about one in 50. If he never smokes, his chances of acquiring cancer of the lung are one in 170 to 190; if he smokes a pack or more of cigarettes a day routinely, he has a one in 15 to 20 chance of developing cancer of the lung. Alarming as these figures are, they are based on present rates, and those rates are rising rapidly.

A year after the analysis of the data at hand which provided the foregoing figures, a second analysis was undertaken—this one based on the 32 months accumulation of death records of the men in the original study group. The results confirmed the earlier findings. In fact, they indicated that the relationships between cigarette smoking and susceptibility to cancer of the lung are decidedly more striking than they appeared to be in the previous investigation. For instance, if attention is restricted to the men whose lung cancers were diagnosed with reasonable certainty, it was found that only two lung cancers occurred during the study interval among the 32,460 men who had never smoked—a standardized rate of 4.9 per 100,000. By contrast, there were 152 deaths from lung cancer among the 107,978 men who had smoked cigarettes regularly at some time—a rate of 145 per 100,000, which is to say that regular cigarette smokers (regardless of amount) died from lung cancer at a rate 29 times higher than did nonsmokers. The rate of death from lung cancer among regular pipe smokers was 10 times greater than that for never-smokers, while the rates for cigar smokers did not differ significantly from those of nonsmokers.

By all odds, and as might be expected, the highest rates of death from cancer of the lung appeared in the group which admitted to smoking two packages of cigarettes or more a day at the time of questioning. These men died of lung cancer at a rate 90 times higher than that of men who had never smoked.

The latest analysis produced information which goes as far as anything has to date to answer the question "If I have been smoking cigarettes for years, will it do me any good to stop?" The data suggest that it will. Among the men who had smoked cigarettes regularly at some time, but who had stopped prior to the investigation, deaths from lung cancer were 14 times more frequent than they were among never-smokers—but only about half as common as they were among men who persisted in smoking cigarettes up to the time the study began.

Thus, although the number of cases available for tabulation is not large enough to draw unequivocal conclusions, it appears that giving up the habit—even after years of cigarette smoking—may reduce the risk of developing lung cancer.

#### 4.

There is in some quarters an unbecoming skepticism of statistics in general and of these remarkably consistent results in particular. By some—a diminishing band, as I see it—the findings are rejected because there is not "laboratory proof." We must remember that far less efficient statistical methods have pointed to direct and effective means of preventing illness many times in the past. The simple observation that milkmaids never got smallpox but usually acquired cowpox as young girls led Jenner to urge cowpox on everyone as a smallpox preventive—and the virtue of vaccination is today denied by no sane man. An earlier and even simpler observation—crude but basically statistical—is credited to ship officers in the days of sail, who noted that during a voyage running to many months, scurvy appeared among their crews if lemons, oranges, or limes were not provisioned, but did not occur when such fruits were consumed in even small quantities. Here, then, was a preventive for a widespread disease of economic importance, and it antedated the discovery of vitamins by a hundred years. In 1848—well before the causative bacterium was identified—a certain Dr. Snow abated the great London cholera epidemic by the incredibly simple device of removing the handle of the Broad Street pump, after he had observed that the greatest plague concentration was in the neighborhood of the pump and that nearly everyone who developed the disease had drunk of its water.

But we are not without some laboratory evidence. By condensing the smoke of burning cigarettes and painting the brown gummy condensates or "tar" on the backs of mice, Drs. Evarts Graham and Ernest Wynder and Miss Adele Croninger produced papillomas—benign tumors regarded as precancerous—in 59 per cent of them, and these tumors progressed to true cancer in 44 per cent. It is true that inhalation experiments using smoke or smoke products have not succeeded in inducing epidermoid cancer (the kind responsible for most of the current increase) in the lungs of test animals. One reason has been that in the usual experiment using whole untreated smoke on short-lived animals, the animals die before they have a chance to show any possible cancer-inciting effects. Second, in consideration of the few inhalation experiments which have actually been carried on long enough to demonstrate any cancer-causing influence which smoke may have, it would have been astonishingly fortuitous had just the right technique been used in applying tobacco smoke in just the right amount, over just the right interval and on just the right tissue of just the right animal.

The problems of producing cancer in the research laboratory are extremely complex and far from understood as yet. What will cause cancer in one species will not necessarily cause it in another. What will cause cancer in one tissue of an animal will not necessarily cause it in another tissue of the same animal. Thus it is conceivable that if tobacco smoke does contain an agent which causes cancer in the lungs of human beings, it may not do so in the lungs or any other organs of a mouse or a guinea pig or a dog. Here it is appropriate to point out that no one has ever succeeded in producing cancer in an experimental animal with chromium or any chromium-containing compound, yet the statistical evidence that chromates can cause cancer of the lung is generally accepted.

By way of mitigating attention to the chief suspect, the statement is sometimes made that if cigarette smoking is involved in causing lung cancer, it is obviously not the only cause. This is true, but our interest at this point is not whether it is the only cause, but whether it is a cause of any moment at all. Since lung cancer affects some who have never smoked and since some smoke a lifetime with impunity, the operation of biological or constitutional factors appears likely. Atmospheric pollutants are in the picture too. But to minimize one factor because there may be many will not dispel the murk. Cigarette smoking is one of many factors under suspicion, and furthermore it is the only one over which the individual can exercise full and personal control.

What is the nature of the proof which is demanded to establish the cancer-causing effect of cigarette smoking? If it is that smoke or another tobacco product must be shown to cause cancer of the lung under conditions of experimental control using living human subjects, then I hope the experiment will never be undertaken. No standards of proof in the entire world of research demand as much as that.

If the statistical evidence cited is not enough, then what experiments may be designed to yield data which will afford proof—proof acceptable to the only judgment we can legitimately rely on: that of scientists who are familiar with the complexities of cancer causation? The smoke condensate from cigarettes has produced epidermoid cancer when painted on the skin of the mouse. With this demonstration as a starting point, a number of directions of inquiry appear to be logical. Will cigarette smoke itself produce cancer in a variety of test animals?

The answer to this question involves inhalation experiments of varying kinds. Again from the starting point, will the smoke condensate cause cancer in animals other than the mouse? Specifically, will it cause cancer of the skin in dogs, in primates, and in man? Is the condensate carcinogenic for tissues other than skin? These questions require exposure of a number of biological systems through inhalation, application, injection, and ingestion. Efforts to identify the specific carcinogens responsible for the cancer-producing effect of the condensate should be undertaken and are indeed under way. These efforts involve fractionation experiments and efforts to demonstrate a possible cancer-causing property of the several fractions. It may well prove to be expedient, after one or more such compounds have been identified, to isolate them and, should new suspected carcinogens be involved, clinch the proof of their carcinogenicity with appropriate biologic tests. If carcinogens are identified in the smoke condensate, it would appear desirable to determine whether they are present in the smoke itself. If so, are they present in the processed cigarette, in the wrapper, in the crude leaf, in the insecticide, or in the additives?

The objectives here are definite. If they are reasonable and generally acceptable to scientists in the appropriate disciplines, what can be done to hasten their achievement? First, the resources with which interested scientists can work must be provided. Second, the scientists themselves can take active steps to create a reciprocating environment in which all investigators working in one or another sector of this frontier will be encouraged to cooperate and communicate with one another.

What shall stewards of the people's welfare do in the meantime?

The American Cancer Society has resolved to support, as its resources permit, research efforts to identify whatever cancer-inciting substances may be in tobacco and its products and to find the means of eliminating them. In the meantime it is committed to setting the facts, as they stand today and as they accumulate, before the people—all the people—of this country. It does not hold that smoking causes cancer of the lung. It does not propose to tell the public not to smoke. It does intend to equip the national conscience with the information by which it can make up its own mind fairly. If time should establish the innocence of tobacco, such a course will prove less blameworthy than failure to suggest caution to smokers and potential smokers of cigarettes today. As one of my doctor friends puts it: If the degree of association which has been established between cancer of the lung and smoking were shown to exist between cancer of the lung, and say, eating spinach, no one would raise a hand against the proscription of spinach from the national diet.