A BRIEF REVIEW

of the

SMOKING—LUNG CANCER THEORY

An Address

by

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For the past six years my colleagues on the Scientific Advisory Board to the Tobacco Industry Research Committee and I have been responsible for the placing of about $3,500,000 in research grants with independent scientists undertaking to study problems, both specific and basic, relating to questions raised about tobacco smoking and health.

In the course of this activity, we have been exposed to and have had to consider an ever-growing mass of research reports relating particularly to the complex problem of lung cancer and all possible suspect factors in its etiology. Some of these reports are directed at tobacco, principally cigarette smoking. In addition, there has been an attempt to involve tobacco in a number of other human ailments and causes of death.

My object here today is not to attempt to convince any of you concerning the relative merits of claims or counter-claims about the effects of tobacco use on human health, particularly in relation to lung cancer. It is rather to discuss fundamental aspects of the cigarette-lung cancer charges, as published or stated from various platforms, in order to show you why many of us believe that the problems of lung cancer causation are not solved, and why we believe medical research will be rendered a disservice, if the case is considered decided or closed, as some insist.

There are three main lines along which data on the relation of tobacco use, particularly cigarette smoking, to lung cancer have been collected and presented. They are statistical, pathological, and animal experimentation.

Statistical Data Inconclusive and Inexact

Statistical data were the first to be presented. They still lead numerically and form the overwhelming majority of published material that bears on the general subject of tobacco and health.

The interest that chiefly stimulated the intensive study of the whole subject was itself a statistical one: The increasing number of recorded deaths from lung cancer during the past 30 or 40 years, particularly among white males.

There was and still is wide divergence of opinion among statisticians

and other scientists concerning what proportion of the recorded increase in lung cancer mortality is *real* and what part is due to improved detection, diagnosis, aging of the population, and procedural factors applied in the classification and reporting of causes of death.

We can be sure of one important fact: The numerical increase in reported lung cancer deaths is not an exact measure of change in the real attack rate. We cannot be sure how much, if any, the actual rate of lung cancer mortality has been increasing.

We do not, however, need to concern ourselves too much on this point, other than being sure we recognize its importance. It will, I am sure, require and receive continuing attention.

The involvement of tobacco use in mortality is based on the statistical association of smoking habits with the rate of death. Such an association has been reported for "excessive" cigarette smoking by a number of epidemiological studies. This is the keystone in the arch of accusations against smoking by those who call it "the major cause" of lung cancer and a large number of other diseases.

Cigarettes Blamed for Centuries-Old Diseases

Causes of death that have been related by statistical studies to excessive cigarette smoking include general mortality; lung cancer, laryngeal cancer, oral cancer, esophageal cancer, stomach cancer, bladder cancer, prostate cancer, malignant lymphomas, and all cancer combined; bronchitis, emphysema, tuberculosis and other respiratory diseases; coronary thrombosis, angina pectoris, coronary artery disease, general arteriosclerosis, hypertension, cerebral vascular disease, peripheral vascular diseases, and general mortality from diseases of the heart and circulation; peptic and duodenal ulcer, and cirrhosis of the liver. You may be interested to hear that other recent medical literature also relates cigarette smoking to eye troubles; nose and ear diseases; miscarriages, sterility, and other reproductive disturbances; and a host of alleged actions on the nervous, endocrine and digestive systems of man.

On the face of it, one's credulity has to be strained to believe that these diseases, most of which are as old as the human race, are now being caused by the cigarette which has become a widespread custom in the past half-century.

This impressive list of diverse and unrelated causes of death thus brings us to the first major area of disagreement among the statistical interpreters of statistics themselves.

One point of view holds that excessive cigarette smoking introduces one or more specific carcinogenic, or cancer-producing, substances. But if this is true, how does one account for the association of cigarette smoking with other diseases? To answer this, another point of view holds that excessive smoking produces that old medical umbrella—"general debility"

—under which so many variable and unexplained afflictions have crouched for years, protected from the chilling rain of scientific definition and analysis.

No Human Carcinogens Found in Tobacco Smoke

The first point of view is disturbed by the failure of all efforts to detect in tobacco smoke any substance known to be carcinogenic to man. The second point of view is disturbed by many things among which one may be mentioned, as follows: General debility is not characteristic of over-weight and over-energetic people. *Cardiovascular disease,* which incidentally has been charged statistically with the *highest numerical* excess of deaths among excessive cigarette smokers, *is* associated clinically with those who are advised to "lose weight" and to "slow down" because of their rapid tempo of living.

There are many other inconsistencies between the actual findings and the kinds of interpretation of statistical results reported by various workers.

Some of these will be discussed briefly for, as I have said, the statistical data are the keystone in the often publicized arch of material accepted by enthusiasts as "proof" of the charges that cigarette smoking is causing many ills. Any habit that is believed to be the major cause of lung cancer and that is blamed as a significant factor in a greatly increased incidence of the wide range of other diseases would indeed be a dragon of such magnitude that Saint George himself might hesitate to tackle it.

However, let us consider certain of the unresolved conflicts of opinion which exist among statisticians themselves.

Conflicting Findings On Inhalers, Non-Inhalers

One of these involves the comparison between inhalers and non-inhalers of cigarette smoke.

Two British investigators found in a reasonably extensive population of doctors *no* difference in lung cancer incidence of any great magnitude between the two categories. What difference they *did* find was in favor of inhalers. They seem to have less lung cancer than the non-inhalers.

A few American investigators believe that there is a greater proportional incidence of lung cancer among inhalers, but have not produced data to establish this theory.

Obviously it seems that someone is wrong. They can't both be right.

Since replies from the British physicians concerning their habits of inhalation were collected in exactly the same way and by the same people who also collected information as to the number of cigarettes smoked, as to the duration of the smoking habit, and as to the periods of interruption of the habit, the degree of accuracy of this information needs verification by further studies. This is all the more essential since a high degree of

quantitative and comparative significance has been given to these figures by many statisticians and propagandists.

Another difference in observational results is found in the effect which continued smoking of cigarettes is supposed to have.

Some data show an unexplained but statistically significant protective effect of cigar and pipe smoking, if these types of tobacco use are superimposed on or added to cigarette smoking, regardless of whether the latter be light, medium or heavy.

The variation in the claimed "excess risk" of lung cancer among cigarette smokers as calculated from statistical studies is another example of conflict.

Contrary to many generalizations made about these reports, they do *not* all show the same thing. Depending upon which study you examine, you will find that the relative risk of lung cancer among cigarette smokers may be no different than that of non-smokers, may be fractionally higher than that of non-smokers, may be three times, four times, five times, six times, nine times—and so on up to 36 times the risk of non-smokers.

Same Statistical Evidence — Lots of Guesses

Similarly, there is a wide difference of opinion concerning the relative quantitative role of cigarette smoking in the etiology of lung cancer, even among those who are crystallized and missionary in their belief in the guilt of smoking.

These estimates, all based on statistical evidence as to how much of the lung cancer incidence can be blamed on smoking, vary from as high as 90 percent or almost totality, downward by degrees to less than 10 percent, or almost nothing. Since the *same* statistical evidence is available to all contestants, it is evident that such guesses are more a reflection of the degree of interpretive enthusiasm which each individual possesses than they are of scientific significance. All the guesses can't be right, and if all but one are wrong, who is to say now which one is right?

These selected examples of conflicting data and interpretations will, I believe, be helpful in establishing a balanced and comprehensive basis for present evaluation of many aspects of statistical investigation.

So will certain others next to be considered.

One of these is the relatively higher mortality among males from all the common respiratory diseases. Some statisticians and epidemiologists accept this as a constitutional and/or genetic difference between the sexes. The largely unbalanced X chromosome in males would provide an increased opportunity for *direct* expression of certain genes which may influence susceptibility. The balanced X chromosomes of the female would decrease this opportunity. Others believe that no real difference exists between the sexes and that when women have smoked as long and as intensively as men they will show an equal mortality from lung cancer.

Two lines of statistical evidence are strongly in favor of the existence of a real sex difference in susceptibility. One is direct and consists of the fact that the lung cancer mortality difference between the sexes has been *widening* in recent years instead of diminishing. On the theory that relatively more and more women are completing the hypothesized cancer-latency period of 20 to 30 or more years of smoking, the gap should *narrow*.

The second line of evidence, which is indirect, is the persistently greater susceptibility of men to other respiratory diseases where exposure of both sexes to infection and other causes is more nearly equal.

Unexplained Differences in Lung Cancer Rates

Further, there are unexplained differences in cigarette smoking-lung cancer calculations as one goes from country to country, from region to region, or from city to city in any given country where such data have been collected. For instance, people in the United States, who smoke 30 percent more cigarettes per capita than the British, have a lung cancer death rate less than half that of England and Wales. The American lung cancer death rate is about the same as that in Denmark and Switzerland, where per capita cigarette smoking is about one-half that in the U. S.

In this country, governmental studies of lung cancer incidence in several major cities show wide variations that cannot be explained by differences, if any, in cigarette smoking usage.

To attempt to reconcile such differences, which disturb them, some statisticians and their assistants have zealously collected cigarette butts and measured them carefully. They have reported shorter butts in Britain than in the United States and feel that this means that our British cousin obtains especially harmful substances from the last part of his cigarette. They thus explain the statistical discrepancy to their own satisfaction.

There still remains the open question, however, as to why migrants from Britain to South Africa and New Zealand have a higher lung cancer incidence than native whites in those countries, even though cigarette smoking is as high or higher among the native-born. Two different and independent reports have shown significant differences in lung cancer rates between the native-born white men and those who immigrated, and these differences are not related to the rate of smoking among these groups. Both authors *do* relate these differences in lung cancer mortality to other environmental exposures sustained in the country of origin.

Turning to animal experimentation, we find an equal or even more finely applied degree of quantitative interpretation. The various relative amounts of residue distilled from tobacco smoke obtained from machine combustion of thousands of cigarettes and then painted on the shaved backs of mice have been used to build up a whole superstructure of estimated degrees of risk of lung cancer in human beings. The animal re-

sults were obtained by use of concentrated chemical material in which no substance known to be carcinogenic to man has been demonstrated. Furthermore, no substances have been detected in this smoke residue which are present in amounts, either singly or in combination, to account for biological activity on the skins of experimental animals. The material has been obtained by methods of smoking which differ in many ways from the process of human smoking. The material has been tested over the entire lifetime of animals often known to be genetically susceptible to cancer. Even so, only a minority of the animals developed skin cancer. This type of animal test for relative pathogenic potentiality frequently has been shown to give positive neoplastic reactions to substances that have been used by and applied to man with impunity for years.

Inhalation Tests with Animals Negative

Uniformly negative results have been reported from smoke inhalation experiments with animals. Those who hold to the tobacco guilt hypothesis ignore or soft pedal this evidence, which involves the use of actual cigarette smoke itself as the challenging agent and the animal lung itself as the target organ. Yet they accept and publicize as supporting evidence the results of applying a machine-made concentrate of smoke to the shaved skin of animals. The scientific status of such selective and discriminative emphasis is open to question. There are increasing numbers of experimental investigators who are doing just that, and who are openly skeptical as to techniques and interpretation.

There is also marked disagreement as to the nature and significance of the metaplastic pulmonary lesions which a minority of pathologists call carcinoma *in situ*. The majority of pathologists who have been interested in lung pathology do not so define these metaplastic changes. Furthermore, these changes are frequently observed in areas of the respiratory system where little or no carcinoma is observed. This shows that they are not definitive of cancer. Second, they occur frequently in cases of pneumonia among adult smokers and non-smokers alike and in young children in whom bronchogenic carcinoma is a rarity. They are, therefore, not specific for smoking.

There are further disagreements among statisticians and pathologists as to the relation of adenocarcinoma of the lung to the smoking problem. Some believe that adenocarcinoma is associated; some that it is not. Some believe that it is possible to identify two clearly distinct histological groups of lung malignancies; others believe that this is not possible. This melange of conflicting interpretation is again selectively screened by advocates of the tobacco guilt hypothesis and the selected favorable material is used as supporting evidence; the "unfavorable" or dissenting results are ignored.

There is also a very definite difference of opinion as to the major or

minor nature of any hypothesized role of tobacco in the etiology of lung cancer. As before stated, some believe that there is a direct, major carcinogenic effect of tobacco. Others, noting the large number of smoke inhalation tests in animals, none of which, in spite of massive exposure, resulted in producting lung cancer, are convinced that if tobacco has any role it is a very minor one. The fact that lung malignancies have been observed in animals following inhalation of oil and gasoline combustion products shows that the animal lung as such *can* be a site of lung cancer. The consistently higher statistical incidence of human lung cancer in urban populations compared with rural is considered as supporting evidence of the need for further study of air pollutants as a potential factor of importance.

Latency Period A Statistical Convenience

Another area of statistical disagreement is the duration of the hypothesized latent period before the carcinogenic changes attributed to smoking are supposed to occur. Estimates vary over a range of from 10 or 15 to 30 or 40 years. Since 90 percent of heavy smokers at age 80 or over do not have lung cancer, and since many individuals report that they started smoking at age 12, there seems to be no valid reason why the latent period should not be extended from early adolescence throughout the life span. This is a great statistical convenience, for it allows the sensational but meaningless statement attributed to one of surgery's most enthusiastic advocates of tobacco guilt: "Every cigarette smoker will die of lung cancer if he doesn't die of something else first."

There are differences also in defining what may properly be classed as "heavy," moderate" or "light" smoking. The "pack a day" criterion, as recorded from the recollection of smokers or their families and friends, is an approximate estimate and not a scientific measurement. It is obvious that an individual who smokes 20 cigarettes per day to the shortest convenient butt length may draw into his mouth an amount of smoke equal to that of a smoker who daily smokes 60 cigarettes down to one-third of their length.

The only thing that smokers of a given number of packs per day have in common—granted that the figures are accurate—is that they lighted the same number of cigarettes. This brings up another device used in some of these studies, that of translating quantities of cigar and pipe tobacco used into terms of packs of cigarettes. This type of non-scientific conjecture merely helps to complicate the differences reported in all the statistical studies between the effects of cigarettes, pipes and cigars!

If one is to understand scientifically the relative activity and physiological importance of the numerous factors involved in the etiology of lung cancer, he is faced with one of the most difficult areas of investigation in the whole field of cancer research.

Other Suspect Factors Exist Besides Smoking

Factors other than smoking *per se* begin to suggest themselves as possible suspects to be considered.

Immediately we find many interesting problems worthy of continued attention and study.

A socio-economic difference has been observed in lung cancer incidence. The lower the economic level, the higher the rate of lung cancer.

Malnutrition and dietary deficiency, already apparently operative to some degree in the etiology of cancer of the buccal cavity and tongue, comprise one matter to be studied. Stress and strain as an unbalancing and continuing element in the life of the individual form another possible element to be kept in mind.

Another is the possible role of previous or current respiratory infectious processes with their accompanying lesions, and disturbances or disruption of the continuity of function of certain areas of the lung. There is an amazingly symmetrical divergence between the curve of recorded increase of lung cancer mortality and the curve of decreasing death rate from respiratory infections. This may or may not prove to be a coincidence. It is certainly worthy of further study. This is especially emphasized by the increase in the lungs of patients with influenza and other lung diseases of the kind of lesions believed by certain pathologists to be potential precursors of lung cancer.

It can be seen that these are all complex matters for definition, measurement and analysis. The human individual *is* complex, however, and so are his motivations and reactions, including his habits. We cannot change these facts. They are an unavoidable part of the problem.

Closed Mind Attitude is Unfortunate

Those who accept the reported statistical association between smoking and lung cancer as proof of a cause and effect relationship often become irked and even abusive when others require experimental evidence and more carefully-controlled clinical and statistical studies. This attitude seems to be unfortunate from at least two points of view.

First, it accepts a superficial standard of scientific proof which cannot safely be applied in determining etiology in such a complex and delicate process as carcinogenesis.

Second, the dogmatic attitude toward smoking produces a feeling of definiteness and conclusiveness which an individual cannot safely apply to his own case even though the theory is advanced with much the same degree of assurance that quite properly establishes the use of a vaccine or other specific for a recognized disease.

Some 20 to 30 years ago, cancer research and therapy were bedeviled and endangered by widespread and irresponsible announcements of

"cures." These claims proved to be inaccurate and premature. In the process, however, false hopes were created, the still unsolved nature of the problem was obscured, and many thousands of individuals died because they trusted part truths or misinformation.

I do not say that the present high-powered and extensive campaign against cigarette smoking as a "cause" of cancer has the same degree of danger as did the claims of cure which proved to be false. I do feel, however, that *all* the evidence on which the conclusions of finality are drawn and on which the campaign is based should always be presented. The continued selection and presentation of only the evidence that supports the smoking theory is neither scientific nor honest. Let the public have *all* the facts in an impersonal and unemotional presentation.

Promotion of Fear Campaign Dangerous

One should not revert to a policy of using *fear* as a lever to activate behavior. Though the dangers of such a policy are apparent in regard to the public, there are some individuals and organizations that have abandoned the honest, objective approach and adopted fear campaigns to advance their objectives. In my opinion a startling example of this "scare" effort is an article entitled "The Growing Horror of Lung Cancer," appearing in a national magazine, that has been accepted and quoted by a large, voluntary health agency supported by donations from the public and supposedly dedicated to a scientific approach to the problem of cancer.

I believe that, from this necessarily limited presentation of some of the complexities and variables which are involved in the etiology of lung cancer, as well as of some of the difficulties and discrepancies in recording and in analyzing its incidence, there is reason to advocate and to continue to practice sound, unbiased, scientific judgment in evaluating the role, if any, that cigarette smoking plays.

In most situations of this sort one is apt to find that differences in the host organism are a major, if not the chief, factor in determining the response to the challenge. There is great need to organize and carry out studies in this field.

During the time that will be needed to establish a sound longitudinal clinical study of sufficient magnitude to determine definitions and secure data to allow a really scientific epidemiological analysis, it is hoped that experimental work on the problem will increase greatly both in extent and in depth. This result will be more likely to be attained if members of the medical profession, no matter what practical procedures they advise, will adopt an unbiased and judicial approach and understanding and tolerance toward those who seek for more knowledge than we now possess before accepting the dictum that the major cause of lung cancer in man is known.