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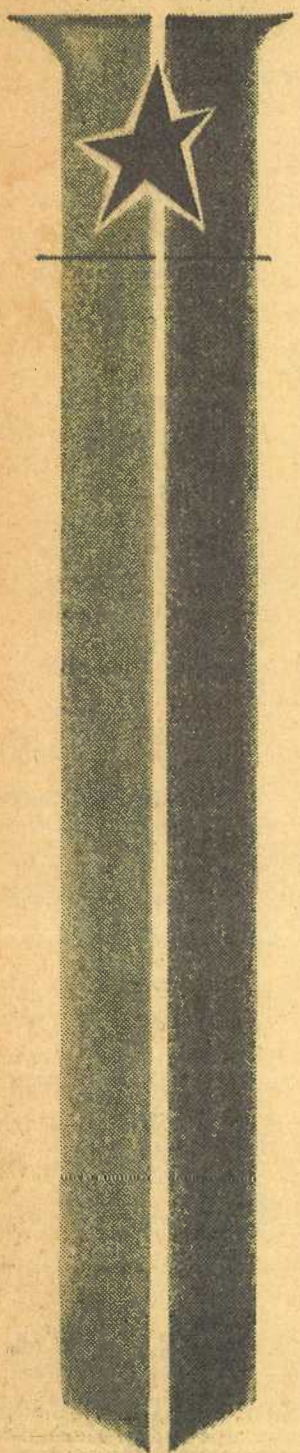


The Cancer Controversy

THE CASE AGAINST THE CIGARETTE

Abraham M. Lilienfeld

Revolt Against Political Mythology

STORM OVER ARGENTINA

Irving L. Horowitz

Christian Citizen began a series of "prayer dinners." These are to continue until all major population centers have been covered.

Christian Citizen may be spreading its arms to embrace all professing Christians, but thus far those who have entered are predominantly of the evangelical sects, and particularly of Von Frellick's own Baptist persuasion. Its board includes Gene Edwards, young Texas evangelist who heads its Southwestern district office; the Reverend Dr. R. L. Decker, pastor of Kansas City's Temple Baptist Church, who heads the regional office there; Dr. Melvin Forney of Philadelphia, head of the Lord's Day Alliance; Dr. William R. Bright of Mound, Minnesota, leader of "Campus Crusade"; J. T. Adams of Sulphur Springs, Texas, organizer of the "Men of Texas" men's choir; Mrs. Julia B. Kohler, president of the Massachusetts W.C.T.U.; the Reverend Dave Breese of Wheaton, Illinois and others.

Von Frellick was born, picturesquely enough, on a log-cabin farm near Miami, Oklahoma, in 1916, the son of German-American parents. His family later moved to Kansas City, and he graduated in 1940 from Oklahoma State University as an architectural engineer. He went at once into independent contracting, but in 1942 enlisted in the Navy, and spent three years as an officer in the Seabees.

After his discharge he entered real estate, sand and gravel supply and road contracting simultaneously, and went broke. He paid off all debts, "though in no way personally responsible," says his official biography. Down to his last $2 bill, which he still displays under the glass cover of his office desk, he landed in Denver in 1953, and after working for others for a short time, relaunched his independent career. Now he controls and operates modern shopping centers at Denver, Amarillo and San Antonio, and is building another at Boulder, Colorado, as well as the $15 million Cinderella at Denver. Von Frellick is obviously a man of drive and organizing skill, and it is likely that his Christian Citizen will raise enough money in $10 initiations and $2 dues to add appreciably to the clamor on the Right for a return to God, States' rights and laissez faire.

The Case Against the Cigarette . . *by Abraham M. Lilienfeld*

Nation readers were alerted early to the controversial question of the relationship between smoking and lung cancer ("Smoking and Lung Cancer," by Dr. Alton Ochsner, May 23, 1953; and, subsequently, an editorial, "Change of Style," April 6, 1957, and "Cigarettes, Cancer and the Campus," by David Cort, August 15, 1959). The following, an authoritative survey of the evidence to date, was written by a former member of a U.S. Study Group on Smoking and Health who is now Chairman of the Department of Chronic Diseases at The Johns Hopkins School of Hygiene and Public Health.—ED.

EARLIER this month, a committee of the Royal College of Physicians of England, headed by Sir Robert Platt, the college's distinguished President, reported that "It's the cigarette smokers who get cancer of the lung. Indeed, those who smoke 25 or 30 cigarettes a day have about 30 times the chance of dying of it that a nonsmoker has" (AP dispatch, March 7). The return of this issue to public prominence might make it profitable to review the scientific evidence on the relationship of cigarette smoking to lung cancer and the interpretation of this relationship.

Probably one of the most striking disease phenomena in the past twenty years has been the marked increase in mortality from lung cancer in the United States and elsewhere. In 1930, the age-adjusted death rate from lung cancer in this country was 3.8 per 100,000; in 1956, the rate was 31.0 and more than 29,000 Americans died of lung cancer in that year. The gravity of the situation is enhanced by the fact that the totality of available diagnostic and therapeutic methods are not very effective: only 5 to 10 per cent of people with lung cancer survive five years after diagnosis.

So marked an increase within so short a period is most probably a result of the introduction of one or more etiological agents into man's environment. In attempting to uncover possible agents, it seemed natural to study inhalants such as tobacco smoke. In 1939, the results of the first of a series of retrospective studies were reported by Muller. In this study, the smoking habits of patients with lung cancer were compared with those of individuals without lung cancer who were selected as controls. It was found that a larger proportion of lung-cancer patients smoked cigarettes than did the controls. Since then, about thirty similar studies have been reported with essentially similar results. One recent study showed that 92 per cent of lung-cancer patients were cigarette smokers as compared to 73 per cent of controls; 53 per cent were *heavy* smokers as compared to 23 per cent of controls. Several of these studies were carried out on female patients with results similar to those found among men.

The association of lung cancer with smoking was further investigated here and in Great Britain by three independent research units who questioned population groups on smoking habits and then followed the groups for several years to determine mortality rates and causes of death. In one such study, conducted by the American Cancer Society, 187,783 white men aged fifty to sixty-nine were followed for forty-four months. Those who never smoked cigarettes had a death rate from lung cancer of 12.8 per 100,000 man-years as compared to a rate of 127.2 for those who had a history of having smoked cigarettes. Also, the death rate increased with the increasing number of cigarettes smoked, while ex-smokers had a lower death rate. On the whole,

these studies have been consistent in indicating that cigarette smokers had about ten times the number of deaths from lung cancer as did nonsmokers. Pipe and cigar smokers had death rates that were only slightly higher than nonsmokers. It is fair to say that there is no disagreement over the fact that a statistical association exists between cigarette smoking and lung cancer. Differences have developed over the interpretation of this association.

THE TWO MAJOR explanations that must be considered are: (1) cigarette smoking *causes* lung cancer (the term "cause" is here used in a pragmatic sense; i.e., we would say that a "cause" is some factor that, if removed from the environment, would result in a decreasing frequency of a particular disease); (2) the association is an *indirect* one, resulting from the existence of a common unknown factor that causes people both to smoke and to develop lung cancer. This explanation is sometimes referred to as the "self-selection" or the "constitutional" hypothesis. Clearly, if this situation exists, lung cancer and cigarette smoking are statistically related *not* on a causal basis, but through the common factor. R. A. Fisher, the noted British statistician, agrees with this hypothesis and argues that the common factor is a genetic one.

The debate over the relationship of cigarette smoking to lung cancer consists essentially of attempts to discriminate between these two hypotheses. What are the available data in support of each?

The first approach to the problem — and the ideal one in that the results would be definitive — would be to carry out experiments in population groups. Theoretically, this could be done in two ways:

¶Establish an experimental group that would smoke and a control group that would not smoke, participants being allocated at random to each group. Such an experiment would have to be launched with preteen-age groups and the groups followed for a number of years to determine their mortality from lung cancer. Needless to say, a test of this kind is quite impractical, although it is the only kind that would convince some investigators of a causal interpretation.

¶One might set up a well-controlled experiment to determine whether cessation of cigarette smoking results in a decrease in the death rate from lung cancer. In this instance, one would start with a group of cigarette smokers, allocating them at random to an experimental group that would stop smoking and to a control group that would continue to smoke. Both groups would then be followed for a number of years to determine their death rates. Again, the possibility of successfully conducting such an experiment is small. I feel, however, that some attempt should be made to determine its feasibility, at least.

THE second general approach is to try to produce lung cancer in animals with cigarette smoke and to determine the biochemical or biophysical mechanisms by means of which cigarette smoking produces lung cancer. To date, attempts to produce lung cancer in animals with cigarette smoke have been unsuccessful. However, it has been possible to produce lung cancer in a dog by the local application of tobacco tar to the mucous membrane lining of the bronchus. Also, several investigators have produced skin cancer in mice, following repeated long-term applications of tobacco tar. While one might question the validity of generalizing from results achieved on mouse skin, which is quite different from the human lung, the results are significant in that they do indicate the presence of a carcinogenic agent in tobacco tar. Several such chemical agents actually have been isolated. Also, experiments of this type could elucidate the mechanisms by which these agents produce cancer and perhaps determine if similar mechanisms are present in humans. Several investigators are now conducting research along these lines.

Related to this experimental approach are histopathological studies which have shown that there is a notably increased frequency of cellular changes, of a kind generally considered to mark early stages in the development of cancer, in the tracheo-bronchial tree of cigarette smokers as compared to nonsmokers. Clearly, the results of these studies are consistent with and strengthen the causal hypothesis.

THE THIRD approach to the problem is epidemiological. Certain types of epidemiological studies can be carried out that would provide data relevant to the two hypotheses under discussion. We can consider three types of such studies.

1. The first type is one in which the distribution of lung cancer among the population, according to such characteristics as age, sex and race, is first determined. Then the distribution of frequency of cigarette smoking, using the same population characteristics, is determined. Finally, the two distributions are compared to discover how far they are consistent with each other. Essentially, this approach attempts to determine whether variations in the distribution of lung cancer in the population can be explained on the basis of variations in the distribution of smoking habits. Here is an aspect that has not been sufficiently studied, but whatever studies have been done along this line indicate that many of the variations in frequency of lung cancer among different population groups are explainable by differences in cigarette-smoking habits. In fact, it is of more than passing interest that a good part of the excess lung-cancer mortality among urban residents is explained by the fact that more urbanites are cigarette smokers than rural residents. But all of the excess cannot be so explained, and therefore air pollution, exposure to certain occupations, or other as yet unknown factors associated with urban living may be of etiological importance.

2. A second type of epidemiological study that could be done is to compare smokers and nonsmokers with respect to as many sociological, biological, etc. characteristics as possible. Essentially, this approach attempts to determine the existence of the possible common factor, since if the smoking-lung cancer association is an *indirect* one, cigarette smokers should differ from nonsmokers with respect to this factor. In such studies, it should be kept in mind that any differences found

between cigarette smokers and nonsmokers must be at least as great as the degree of association of cigarette smoking with lung cancer. Otherwise, these differences cannot be shown to be of importance in the etiology of lung cancer. Also, it then becomes necessary to determine whether the characteristics which differentiate cigarette smokers from nonsmokers are independently related to lung cancer before they can be assumed to be the common factor. (Of course, in reasoning in this manner, we run the risk of overlooking the pertinent common factor simply because we just do not know what to look for. But this is a risk common to most scientific research.)

On the other hand, in such studies, the more nearly similar cigarette smokers and nonsmokers are shown to be, the less likely is it that the association is merely indirect.

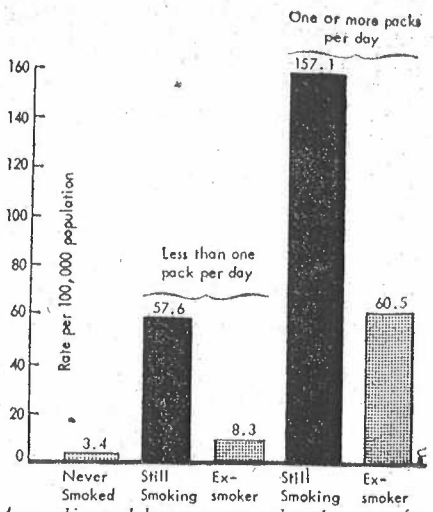
SEVERAL studies have indicated differences between cigarette smokers and nonsmokers. Cigarette smokers consume more alcohol, more black coffee, change jobs more often, engage in more athletics and respond differently on an emotional questionnaire. They are more likely to have had at least one parent with hypertension or coronary disease, and to have more native-born parents. However, in none of these relationships is the degree of difference between cigarette smokers and nonsmokers sufficiently great (although statistically significant) to account reasonably for the degree of association of cigarette smoking and lung cancer. To date, the results of these studies *decrease* the plausibility of the indirect-association theory.

3. A third type of epidemiological approach consists of attempting to discover other etiological agents. Even if the causal association is accepted, it does not mean that cigarette smoking is the *only* causal agent; nonsmokers, too, develop lung cancer. By means of epidemiological studies and the determination of the nature of other etiological factors, it may be possible to develop reasonable explanations for *all* cases of lung cancer. At present, there are leads upon which further inquiries can be based. Some studies definitely incriminate certain types of occupational exposures, such as in the chromate industry. There is an increasing incidence of lung cancer with decreasing socio-economic status (which may or may not be related to occupation). Several studies have indicated an increased risk of lung cancer among the foreign born. There exists a real need for further epidemiological studies in lung cancer.

The results of such studies to date tend, in general, to make the *causal* interpretation more likely and the *indirect* association less likely. Putting all the evidence together, it seems that the causal hypothesis has a high probability of truth. Despite the evidence, however, objections have been raised with respect to certain aspects of the problem.

IF CIGARETTE smoking causes lung cancer as a result of a carcinogenic substance in tobacco, one would expect that the risk of developing lung cancer should be higher among inhalers than among noninhalers. In the retrospective study by Doll and Hill, no differences between inhalers and noninhalers were observed—a major point made by R. A. Fisher. However, three more recent studies have reported an excess risk for lung cancer for cigarette-smoke inhalers. It isn't clear as to why the results of Doll and Hill differ from the others, but the weight of present evidence would seem to be a suitable answer to Fisher's strictures.

Another objection raised against the causal hypothesis is that not all cigarette smokers develop lung cancer. Actually, the lifetime risk of dying from lung cancer is about one in ten for heavy cigarette smokers. The lack of a complete correspondence between an etiological agent and a disease is not uncommon in human illnesses. Not all those who ingest contaminated food or water develop illnesses caused by the contaminants. In industries where there is exposure to various toxic agents, not all those exposed develop diseases caused by these agents. There exist factors that influence the susceptibility of an individual to such exogenous agents. In only a few diseases do we have sufficient information to define, measure or detect the state of susceptibility. More research in this area would be welcome, but



Age-adjusted lung-cancer death rates for smokers, ex-smokers (persons who have given up smoking for at least ten years) and nonsmokers.

—American Cancer Society Study

it must be noted that the control of a disease does not need to wait for determinations of this kind.

Of possible importance to the question of susceptibility are the sex differences in mortality from lung cancer: men have a much higher risk than women. Opinions vary as to whether the difference is explainable by variations in cigarette-smoking habits — including inhalation — or whether there are constitutional characteristics of women which decrease their susceptibility to environmental causative agents. Further research is needed.

One of the most frequent objections to the causal hypothesis is that the statistical relationship between cigarette smoking and lung cancer is non-specific. This is based on the observations, in the prospective studies, that cigarette smoking is related not only to lung cancer, but also to chronic bronchitis, cancer of the esophagus, peptic ulcer and coronary heart disease. However, the relationship between cigarette smoking and lung cancer is outstanding; in these studies, cigarette smokers had a tenfold excess risk of dying from lung cancer, as compared to nonsmokers, in contradistinction to a 3.3-fold risk for chronic bronchitis, a 2.8-fold risk for peptic ulcer and a 1.6-fold risk for chronic heart disease. It would seem reasonable to take the degree of relationship into account in evaluating specificity. Also, we must consider that tobacco,

a complex substance, may well contain agents that may be of etiological importance in many diseases. And there is no biological necessity for one agent to cause only one disease. Excessive exposure to ionizing radiation may result in gastro-intestinal disturbances, cancers of a variety of organs (thyroid, ovary, bone and others), nephrosclerosis and other diseases. Yet, this fact has not been a deterrent to inferring a causal relationship.

There are some who feel that a causative explanation is not acceptable because, at the moment, we do not know the "cause" of cancer. It appears that by "cause" is meant that all of the detailed mechanisms, in terms of cellular biochemistry or biophysics, have not been worked out so that we understand completely how a normal cell becomes a cancer cell. However, such criteria would make invalid generally accepted causative interpretations of various types of cancer resulting from exposures to toxic agents in industry. No one doubts that exposure to various aniline dyes is a cause of bladder cancer and that chromate workers have a higher risk of developing lung cancer. Absence of data on cellular mechanisms has not deferred the application of preventive measures to decrease the risk of cancer from these exposures. In fact, it is well to point out that the evidence upon which causal relationships in industry have been determined is of the same kind and even less extensive than is already available with respect to cigarette smoking and lung cancer!

THE DECISION as to the amount and type of evidence necessary to prove a causal interpretation is dependent on the psychological outlook of the person making the decision. A laboratory scientist without direct responsibility for the health of the public may well desire so much evidence that he can say that his causal interpretation is 99 per cent correct; he wants to be absolutely certain. On the other hand, a public health official may feel that he does not require absolute proof before preventive action is indicated. In his case, a 55 per cent chance of being right may provide a sufficient basis for preventive action. This viewpoint has been expressed best by the noted biostatistician, Edwin B. Wilson, who stated:

> One of the difficulties of following the mathematical fraternity is that one may adopt some of their conventions too literally . . . and they have a way of using $P = .05$ as a standard significant level, which is all right if understood, but the business man, the investor, the weather forecaster, the executive or the card player who waited for that degree of significance would be so out of the game as to be without a livelihood. Theodore Roosevelt is said to have remarked that an executive who made four right decisions out of seven was good — a "confidence" of .556 instead of .95. For practical purposes we have to take chances with our inferences, and actually no matter how meticulous our probability calculations, we have to take chances on those probabilities.

THOSE WITH responsibilities for the public health have reviewed the evidence and believe that it is most reasonably interpreted as indicating that cigarette smoking is a major causative factor in the increasing incidence of lung carcinoma. In addition to the Royal College of Physicians mentioned earlier, the Public Health Cancer Association (U.S.A.), the Ministry of Health of England and Wales, the Medical Research Council of Great Britain, the Netherlands Ministry of Social Affairs and Public Health, the State Medical Research Council of Sweden, the American Public Health Association and the Surgeon General of the U.S. Public Health Service have concurred in this decision. A study group convened by the World Health Organization to make recommendations on desirable avenues of research in lung-cancer epidemiology made a series of recommendations on types of studies needed to fill in existing gaps in knowledge. However, the group was careful "to call attention to the fact that existing knowledge of the etiology of lung cancer is already sufficiently well established to justify prophylactic action aimed at reducing exposure to known etiological factors."

The kinds of preventive action called for have never been systematically developed by any group or agency. There is a general feeling that it would be difficult, if not impossible, to motivate adult smokers to stop smoking. The Royal College of Physicians recommended that (1) special clinics be established to help those who find it hard to give up the habit and (2) the price of cigarettes be increased to encourage people either to give them up or to turn to less harmful pipe or cigar smoking.

That smoking habits can change is indicated by the results of a survey of Massachusetts physicians in 1954 and 1957 by Snegireff and Lombard: in 1954, about 52 per cent of the physicians smoked cigarettes compared with 39 per cent in 1959; in 1954, 34 per cent were nonsmokers as compared to 45 per cent in 1959. Perhaps large-scale publicity campaigns might have an effect, but they would have to counteract the approximately $146 million spent annually in advertising by the six major tobacco companies. Would it be easier, perhaps, to influence the future habits of teen-agers than the fixed habits of adults? Here again, one is up against what Dr. Shimkin of the National Cancer Institute calls the "shameful appeals from tobacco advertising such as those which equate smoking with bravery, sexual virility and social status" (*Advertising Age*, Jan. 29, 1962). It is astonishing to find that one major cigarette company actually has 165 undergraduate representatives serving on college campuses throughout the country (*New York Times*, Oct. 20, 1960). Doesn't the government and the tobacco industry have some obligation to eliminate or curtail this amount and type of advertising?

The best means of control is probably dependent on the results of further research in which the harmful components of tobacco would be isolated, removed or counteracted. Another approach that has not received much consideration relates to the problem of susceptibility. If we could learn to identify individuals who are particularly susceptible to lung cancer when exposed to environmental agents, it might be possible to convince them, at least, that they ought to quit smoking cigarettes.