An Analysis of the Cigarette
and
Lung Cancer Theory*

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Author's Summary

Those who advocate fervently the supposed causative importance of cigarettes in lung cancer seem to have an almost evangelical attitude and are remarkably oblivious to the fact that virtually the entire basis on which this belief rests is statistical.

A review of evidence fails to show a cause and effect relationship. Numerous studies from different parts of the world show other factors that may be importantly related to lung cancer.

Mouse painting experiments cannot be applied to the experience of human cigarette smoking. Based on the amounts of concentrated cigarette smoke condensates applied by Wynder to a small area of a mouse's back to induce mouse skin cancer, a man would have to smoke at least 100,000 cigarettes daily to get an equivalent exposure to his lungs. Again, using Wynder's own figures that reducing the dose by half fails to induce mouse skin cancer, a man could theoretically smoke 50,000 cigarettes daily without danger of lung cancer from smoking. This demonstrates the absurdity of trying to relate to man any dosage calculations derived from mouse experiments.

Discrepancies and fallacies in the cigarette theory are shown, even from those studies often cited in the attempt to incriminate cigarettes. For example, an English statistical study intended to relate smoking to lung cancer showed that moderate smoking was actually more prevalent among the group without lung cancer than it was among lung cancer patients.

The percentage of men over women having lung cancer is growing, rather than decreasing as would be expected in view of the increased use of cigarettes by women, if the cigarette-lung cancer theory is correct.

Studies point to a relationship between social and economic status and lung cancer. Unless one assumes cigarette smoking is far more prevalent in the lowest economic groups—an assumption that is not supported—factors other than smoking are involved.

Several errors concerning claimed causation of disease based on statistical associations are cited. Tobacco was once considered the principal offender as a causative agent in cancer of the mouth. It has since been demonstrated that cancer of the mouth is attended by a severe nutritional deficiency in the great majority of cases, and the tobacco theory has been virtually discarded.

There is considerable doubt whether the incidence of lung cancer is actually increasing. The importance of improved diagnosis and better recognition is shown by a recent study in a new facility in East Pakistan. Examinations revealed 20 cases of lung cancer, predominantly in male manual workers in older age groups, following the pattern in other parts of the world. Of these cases, 14 had never smoked, four were occasional smokers, and only two were heavy smokers.

The urban-rural difference in lung cancer incidence is not consistent with the cigarette theory. Per capita consumption of cigarettes in the states of Idaho and New York is nearly the same; yet the lung cancer death rate in New York is four times greater than in Idaho. Smoking habits in Charlotte, N. C., are little different from those of other comparable communities; yet Charlotte has a lung cancer mortality ratio of about one-third of the national average and less than a fourth of some heavy industrialized areas.

Using various air pollutants, including products merely filtered out of the air in Los Angeles, one group of investigators produced considerably more convincing evidence of cancer-producing ability for these substances in mice—for what it may be worth—than did the Wynder experiment. In some of these tests, they used a lesser dosage, weight for weight, in a year than Wynder used in his tobacco paintings in a week.

In summary, the total evidence reviewed fails to establish any sound basis on which a causative influence may be assigned to cigarette smoking in inducing human cancer of the lung.

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Source: http://industrydocuments.library.ucsf.edu/tobacco/docs/lyhv0041
Full Statement

My name is Ian G. Macdonald. I am a Doctor of Medicine, having received my M.D. Degree from McGill University in 1928, and am Clinical Professor of Surgery at the University of Southern California, School of Medicine, where I have also been coordinator of cancer teaching for the past 10 years. I hold membership in the American Association for Cancer Research, and in a number of national surgical and other medical societies. I have been engaged in the treatment of cancer and allied diseases since 1935, and am certified by the American Board of Radiology (in Radiation Therapy).

I am a member of the National Board of Directors of the American Cancer Society, and am past President of the California Division of that Society. I am Chairman of the Sub-Committee on Cancer, Committee on Research of the American Medical Association.

The constant reiteration of the claim that cigarette smoking is one of the most important causes, if not the most important cause of lung cancer, has persuaded many that a cause and effect relationship has actually been established. A poll of public opinion by the American Institute of Public Opinion reported in the newspapers for July 21, states that 50% of the general public believes that cigarette smoking is one of the causes of lung cancer. Those who advocate fervently the supposed causative importance of cigarettes in this disease seem to have an almost evangelical attitude, and are remarkably oblivious of the fact that virtually the entire basis on which this belief rests is statistical.

Although there is an apparent association between cigarette smoking and lung cancer, a review of the total evidence fails to establish a cause and effect relationship.

In discussing this particular problem, Berkson, biometrician at the Mayo Clinic has commented as follows: "(I am not affected by) the considerable number of statistical studies published...showing an association between smoking and cancer of the lungs. On the contrary, undeviating consistency of statistical results all in support of the same conclusion is in some circumstances the hallmark of spurious statistical correlation. If correlation is produced by some elements of the statistical procedure itself, it is almost inevitable that the correlation will appear whenever the statistical procedure is used." It should be unnecessary, but probably is not, to say that things which are connected by a cause and effect relationship will show a high degree of correlation statistically, but that such high degree of correlation between two things does not necessarily mean a causal relationship between them.

Cancer Is Complex

Cancer is a complex group of diseases of extremely disparate manifestations of abnormal growth of the tissues of the individual in whom the disease arises. A fundamental definition of cancer is an abnormality of growth of cells resulting from a disturbance in the extremely delicate system of check and balance which, under normal conditions, allows the body to replace worn out cells or to repair effectively the result of injury of various sorts. In general, the possibility of a given individual developing cancer depends upon two basic factors:

1. The capacity of the individual to respond to unfavorable influences by developing cancer, and this capacity, or the lack of the capacity, is now accepted by many as being genetically determined, or due to hereditary tendencies.

2. The exposure of the individual to environmental factors which, in the susceptible individual, may eventually result in the degree of abnormal growth which manifests itself as cancer.

Although we have limited information as to some of the genetic factors involved, and although we have considerable information concerning the predisposing environmental influences which may lead to cancer, we are ignorant still of the actual trigger mechanism which sets off the cancerous process in any given individual.

Trigger Mechanism

A commonplace example is found in cancer of the skin. The genetic influence of importance is the character of the individual's skin; the person with thin, delicate skin usually seen in blondes and redheads is extremely sensitive to the environmental agent, which in this instance is sunshine, or at least the ultraviolet fraction of solar radiation. Another fact of importance is that people without sensitive skin structure if exposed over a long period of years to excessive amounts of sunshine have about the same hazard of developing skin cancer as does the person with "redhead skin" who limits his exposure. This will emphasize another point, that an excessive amount of a potentially cancer producing substance over a long period of time may make the individual who otherwise would have been resistant become as susceptible as a sensitive individual. In other words, three separate considerations are involved; sensitivity of the individual, exposure to the possible cancer producing substance, and the duration of exposure. There are hundreds of thousands of persons in our population who develop evidence of abnormal changes in the skin from exposure to the sun and wind, either by reason of sensitivity or long exposure, such as in farmers and sailors and ranchers; yet for every hundred people who develop the warty, scaling patches of abnormality there are only 4 or 5 who actually develop skin cancer even if they live to be well beyond the biblical three score and ten years. Thus we are aware of factors of individual inherited sensitivity and of the most important single environ-
mental influence which combine to create the hazard of skin cancer, yet we do not have any understanding of the trigger mechanism which sets off actual skin cancer in one person.

One further generalization appears to be worthy of mention in our effort to establish a general understanding of the cancerous process. Factors which are found rather consistently in the background of certain individuals with certain types of cancer may contribute directly to the initiation of the cancerous change, or there may be evidence of some other factor which is actually the predisposing agent. As an example, women who have their first child by the age of 18 and who complete childbearing by age 25 have a distinctly greater hazard of cancer of the uterine cervix, but these factors are far more common in girls who grow up in less favorable economic situations and so the increased incidence of growths in the cervix may be a reflection of poor nutrition rather than early childbearing.

In other words, the factor which is first discovered by statistical studies as being in excess in the background of the individual developing cancer may simply indicate the presence, or even the absence, of some other factor which is actually of predisposing or causative significance.

Multiple Factors Seen

There is a growing body of evidence in the past decade or more to indicate that multiple factors are operative in setting the stage for a considerable variety of cancers in man. There is a rather small group of human cancers in which only a single environmental agent is apparent as a predisposing cause of any significance; more commonly there are two or more separate factors frequently of entirely different nature which combine to increase the likelihood of cancer developing in the individual. This is the principle referred to as cocarcinogenesis, indicating the inability of a single agent to produce cancer, but when combined with another or other agents a cumulative effect is created which may lead to the development of cancer. Some of these factors are extremely weak carcinogens, or predisposing agents to cancer. As in experimental animals, some of them when administered in large excess cannot alone produce any semblance of cancer, while their combination in a relatively modest degree with other agents may produce cancer in the susceptible individual.

There have been prior errors concerning causation of disease due to statistical association. During the second and even the third decade of this century, medical textbooks referred to a certain form of cirrhosis of the liver as being "alcoholic" cirrhosis, as practically 9 out of 10 individuals with this type of liver disease could be demonstrated as having been excessive users of alcohol over long periods of years. However, it was also noted, even by those who were most convinced of the causative role of alcohol in this disease, that it did occur at times in individuals who apparently had never been addicted to alcohol, and even in representatives of the clergy in whom a non-alcoholic history could be established.

For some years now it has been established that what was formerly regarded as "alcoholic" cirrhosis is not due to excessive alcohol consumption, but due to a nutritional deficiency.

The high incidence of primary cancer of the liver in certain natives of South Africa and in inhabitants of the Malayan Peninsula was originally thought to be due to environmental exposure; eventually it was shown with little room for doubt that the causative background of cancer of the liver in these individuals arose from dietary deficiencies rather than from exposure to unfavorable environmental influences.

Tobacco Discounted by Study

In the latter part of the last century dire warnings were broadcast concerning the rising incidence of cancer of the mouth, citing statistical evidence that tobacco was the principal offender as a causative agent. Some of the individuals who corresponded to the present evangelistic statistical exponents concerning lung cancer advocated a severe restrictive program on the use of tobacco in order that cancer of the mouth could be diminished. In the years that have followed it has been demonstrated that cancer of the mouth is attended by a severe nutritional deficiency in the great majority of individuals with this group of cancers. Tobacco has now been relegated, by all but the most feverish of the anti-tobacco apostles, to an extremely minor role if, indeed, it occupies any position of causative significance.

One of the principal arguments that smoking is responsible for an assorted increasing mortality from cancer of the lung is based on the gradually rising mortality statistics for lung cancer. It is more than proper to offer some inquiry as to the validity, or at least the degree of the increase in cancer of the lung. It is a striking fact that from 1900 to 1956 there has been a reduction in crude death rates from principal respiratory diseases from 430 to 57 per hundred thousand (U.S.P.H.S. Vital Statistics). When one considers that reasonably exact measures for diagnosis of lung cancer have become available only recently, it is obvious that many of the deaths in the earlier decades of this century which actually were due to lung cancer were recorded in vital statistics as due to pneumonia, influenza, tuberculosis, etc. If one will accept that this error of past decades was as little as 5%, this adjustment would show that there has been no real increase in lung cancer during this century.

Question of Real Increase

A number of investigators have drawn attention to the questionable validity of the figures usually quoted
in support of the increase in cancer of the lung. One authoritative voice is that of Dr. Paul E. Steiner, Professor of Pathology at the University of Chicago, who is generally regarded in the medical profession as one of the outstanding authorities in cancer research and epidemiology. Steiner remarks that an increase in frequency in lung cancer is reported in most clinical studies, in some mortality surveys, but in very few autopsy studies. His observations are such as to deserve quotation: "Great improvement has occurred in recent decades in the clinical diagnosis of lung cancer but accuracy in the autopsy recognition of the natural types has undergone little change, having started from a much higher level." These facts cast doubt on whether the increase is disproportionate to other cancers. Even in the autopsy studies, reported increases may not be real but represent merely a shift in the type of material that the clinical departments send to the autopsy room. While much has been said of the increase in lung cancer relative to other types, Steiner reports that in St. Louis from 1935 to 1950 in 12,443 autopsies lung cancer had increased from 1.5 to 1.9 of 2.5% of all autopsies in the three 5-year periods, but that two other types of cancer, those at the pancreas and breast had increased nearly as much as that of the lung, and that all cancers combined had increased from 16.8 to 20.6% of all autopsies during the period under study.

In summary, one may state that while most of the reports of studies based on the diagnoses of lung cancer made during life show an increase, studies based on autopsies vary, some showing an apparent increase and others showing no increase. Accuracy of diagnosis at post-mortem examination has changed very little since 1900, but the accuracy of clinical diagnosis has greatly improved. Considering these facts, an increase in lung cancer disproportionate to that for all or selected types of cancer has not been demonstrated in most geographical regions, and perhaps even in none.

The main evidence claiming that smoking causes lung cancer is based on statistical surveys here and abroad.

Geographical Disparities

There are a number of geographical disparities related to tobacco consumption which seem to invalidate the suggestion that cigarette smoking is a causative factor. In Australia for example, from 1949 to 1951, the tobacco consumption averaged 4.7 to 4.9 pounds per capita, compared with 5 pounds per head in the United Kingdom; in Australia the incidence of lung cancer was 13.3 per 100,000 as against 55.5 in the United Kingdom; in the 55-64 age group the Australians had 30.5 cases per 100,000 as against the United Kingdom's figure of 111.6 per 100,000. To take an example closer to home, in a recent year 2,003 tax-paid cigarettes were sold per person in Idaho compared to 2,319 tax-paid cigarettes per capita in New York, but the lung cancer death rate in New York was four times greater than that in Idaho. The degree of difference in industrialization in New York and Idaho is well known. Further comment on the factors of urbanization and industrialization will be made later.

It seems apropos to inject here a report from the Medical College Hospital in East Pakistan. During an 18-month study involving 362 cases of pulmonary disease, 20 cases of cancer of the lung were found. The sex, age and occupational distribution corresponded to reports elsewhere; namely, predominance in males, occurrence in late adult life and preponderance of manual workers. All of the cases but two came from rural areas where alleged carcinogens from tarred roads and automobiles were conspicuously absent. Even more striking, of the 20 cases there were 14 who had never smoked, four were occasional smokers, and only two were heavy smokers.

Causation Complicated

The causation of lung cancer is much more complicated than the over-simplified thesis that it is due to cigarette smoking. The data advanced by those who are mesmerized by statistics includes the English findings offered by Doll and Hill. Their controls (without lung cancer) actually contained more subjects in the moderate smoking group than there were lung cancer patients in that moderate smoking group. Their figures thus show that moderate smoking is actually commoner in persons without lung cancer. Even these data may indicate smoking to be a harmless pastime up to 24 cigarettes per day. One could modify an old slogan: a pack a day keeps lung cancer away.

Still another interesting fact in the data collected by English investigators concerns the individual habits of inhalation of cigarette smoke. Many proponents of the cigarette-lung cancer theory have speculated that cigarette smokers inhale more than other types of smokers, thus accounting for the excess of lung cancer in users of cigarettes. Yet Doll and Hill's figures showed that cancer of the lung was more common in cigarette smokers who did not inhale than in those who did inhale.

Another curious finding advanced by the advocates of cigarette smoking producing lung cancer is the fact that the dilution of cigarette smoking by some use of cigars and pipes materially decreases the probability of lung cancer. This seems to be without reference to the degree of moderation or the excessiveness with which the individual uses cigarettes along with the cigar and/or pipe. If cigarettes are carcinogenic they surely should be so whether accompanied by tobacco in other forms or not. It is an insult to reason to believe that two men who indulge equally in cigarettes will have a different chance of lung cancer simply because one periodically adds to his cigarette smoking the use of tobacco in another form.
Male-to-Female Ratio

Another fallacy in the theory that cigarettes have a causal relationship to cancer of the lung is shown by the difference in the relative incidence of lung cancer in males and females. Long before cigarettes were thought to produce the dramatic increase in lung cancer emphasized by the evangelistic statisticians, the ratio of lung cancer in males to females was in the range of 1.5 to 1 and in some areas almost 1.1. In the intervening period disparity in incidence of lung cancer has constantly increased until, for the U.S. at large, it is approximately one female to five males, and in some areas such as Upper New York State, it is in a ratio of one female to seven males. During this period cigarette smoking by females has constantly increased, and a recent study of patterns of smoking by the U.S. Public Health Service indicated that slightly over 40% of women smoke or have smoked cigarettes since 1930. There has been at least a 25-year period during which women have been exposed to the possible causative effect of cigarette smoking. If there be any such effects, and nevertheless the disparity of incidence of lung cancer as compared with the male continues to widen.

An opposite pattern of incidence of lung cancer is demonstrated by some racial groups, and one notable example is the high frequency of lung cancer in Mexican women dying in the Los Angeles area, as reported by Steiner. In autopsies performed at the Los Angeles County Hospital from 1918 to 1947, the Caucasoid and Mexican were the largest of various racial groups involved. Mexican men had only slightly more lung cancer than Caucasoid males, but Mexican females had significantly more lung cancer than Caucasoid females and nearly as much as their male counterparts. Nevertheless, a rough survey of patterns of cigarette smoking among older Mexican women in Los Angeles (of lung cancer age) shows that their use of cigarettes is less than that of corresponding Caucasoid groups.

If cigarette smoking were a real and causative factor in lung cancer, the relative incidence in men and women should be approaching parity instead of becoming more disparate, as is the actual situation. Knowing that lung cancer is predominantly a male disease, there should be a correlation of consumption of cigarettes by males with the "increase" in incidence of lung cancer. However, much of the increase in cigarette consumption since 1930 has been due to the increasing use of cigarettes by women, and although there are no accurate figures available, our best attempts to evaluate this part of the problem indicate that about one-half of the U.S. increase in cigarette sales has been due to their increased use by women. Moreover, the actual increased use of cigarettes by men, allowing for increased use by women, is nowhere nearly proportionate to the alleged increase in lung cancer rates in men.

It is timely now to inject some data concerning cigarette consumption and lung cancer in the United States as compared with England and Wales. From 1920 to 1950 the consumption of cigarettes expressed in pounds per capita increased in England and Wales from 1.6 pounds to 3.6 pounds, while the lung cancer rate was increasing from 17.2 to 72.7 per 100,000. In the United States a vastly greater increase in cigarette consumption took place in this 30-year period, or from 1.6 pounds to 6.3 pounds per capita, but the lung cancer rate increased only from 6.2 to 31.5 per 100,000.

Other factors in the environment have been studied and reported as showing an association with the increased incidence and death rate of lung cancer. Dr. Richard H. Sweet, one of the country's outstanding thoracic surgeons, recently commented that the concentration of effort being put forth to prove a causal relationship of cigarettes to lung cancer, has resulted in neglect of these other factors of equal or greater importance. Hammond has published data showing the correlation of lung cancer with the increase in mileage of state asphalt highways and in the national consumption of motor fuel, both of which are considerably greater in relative increase than cigarettes. Fuel oil sales and motor vehicle registrations also paralleled the increase in lung cancer. There have also been similar sharp increases in the production or consumption of cancer-related industrial chemicals over the same period of time, such as carbon black, petroleum, coal tar, asbestos, arsenic and chromite. All of these factors contribute to the greater degree of air pollution in urban areas and constitute the most reasonable explanation for the difference in the incidence of lung cancer in urban and rural areas.

Incidence Higher Among Poor

Some other associations of more esoteric nature can be offered. One is the fact that the English investigator Dr. Percy Stocks, as quoted by Steiner, shows a negative correlation between the mortality from cancer of the lung and the number of hours of sunshine. Several studies have demonstrated a relationship in the social and economic status and lung cancer. These include studies in New Haven, Conn., reported by Cohart, where the incidence of lung cancer was more than 40% greater among the poor than among more fortunate economic groups. Cohart concluded that unless one could assume that cigarette smoking is inversely related to economic status, and this is an assumption that probably cannot be supported, it is reasonable to conclude that important environmental factors other than cigarette smoking are contributory to lung cancer. Clemmessen and Nielsen reported that there was a significant excess of lung cancer in the male population of the poorer classes in Copenhagen. There have been several investigators who ascribe importance to the co-existence of old healed tuberculosis and lung cancer. Some observers suggest that, as treat-
ment of tuberculosis improved, those who were enabled to survive are now, years later, the persons highly susceptible to the development of cancer of the lungs as they reach the cancer age. On this theory, one such investigator (Woodruff) made the prediction in 1955 that the increasing incidence of lung cancer should reach a plateau, and within a few years actually begin to decline. Present figures indicate that the prediction is proving sound.

Beer and Milk

Figures indicating two other correlations which at first glance may seem absurd are offered by Percy Stocks. He showed a distinct correlation of beer drinking and increased rates of lung cancer, and a negative association for the drinking of milk and lung cancer. It is entirely possible that these findings indicate a nutritional background which may be of importance in the development of lung cancer, just as nutritional defects are important in cancer of the mouth and cirrhosis of the liver.

Differences in lung cancer rates in urban and rural areas are consistently found. Several investigators have concluded that residence and employment in urban areas with constantly increasing industrialization constitute more significant and reasonable associations with lung cancer than smoking.

The adjusted mortality rate for cancer of the lung for white males in the U.S. for 1948-49 was 22.3 per 100,000 in urban areas and only 12.3 in rural areas. A review of comparative death rates from lung cancer in various communities in the United States also offers a striking demonstration of the apparent importance of industrialization. For example, it needs no statistician or expert in sociology to realize that the smoking habits of residents of Charlotte, N. C., are little different from those of other comparable communities in the Eastern part of the country. Yet Charlotte has a lung cancer standardized mortality ratio of only 32 per 100,000, compared to a national average of 100, and compared to various heavily industrialized areas that run as high as 137. It has been estimated that six tons of tarry material fall on each square mile of Manhattan every year, and in English towns the number of lung cancer deaths has been observed to increase in proportion to the number of chimneys per acre in the towns studied.

Men and Mice

From an experimental standpoint, highly concentrated extracts of tobacco tars have been applied on the skin of mice after shaving, by Wynder. Before offering some detailed comments on this doubtful activity, it is proper to emphasize that mouse skin cancer bears no relationship to human cancer, and this is admitted by those who have done the experiments. The lungs and the skin have different origins in development of the animal, and it cannot be assumed that they will react the same way to the same irritant. Still further, mice and men are completely unlike in their response or lack of response to certain agents. For example, cancer of the breast can be produced in a high percentage of mice of certain strains by the use of estrogens (female sex hormone) but intensive use of the same hormone over a long period of years in female monkeys failed to produce a single cancer of the breast or any other organ. It is thus proper to make the following generalizations concerning this particular problem:

a. The demonstration of the production of cancer by an agent in a mouse cannot be accepted as valid evidence of a similar property in men, particularly if the experiment cannot be repeated successfully in higher mammals, which has not been done in the instance of tobacco tars.

b. No satisfactory approach to an equivalent of human lung cancer has been produced in animals after exposure to concentrated doses of tobacco smoke produced by smoking machines.

Analogy to Man Denied

In spite of the fallacies of this particular experimental work, there are other reasons for denying any real analogy with the situation of smoking in the human. This denial is based on the following:

1. An English investigator (Wright) exposed 160 mice for 18 months to cigarette smoke, that is for half of their life span. The smoking mice actually lived longer than the non-smoking mice.

2. Another British investigator (Campbell) observed an increase in lung tumor rate in mice from 8% to 80% when they were subjected to prolonged inhalation of dust from roads with a 2% content of tar.

3. An attempt to compare the amount of cigarette smoking by a human to equal the exposure of the skin of mice in the experiments where concentrated tobacco tar was used points up the absurdity of the comparison. Extrapolating the concentration of tar on the small area of the mouse's skin to an equivalent concentration on the large area of the lung of men, I estimate that a man would have to smoke over 100,000 cigarettes a day to equal the dose Wynder gave his mice. Indeed, Wynder has told this committee (Page 149) that when his dose is cut in half, no tumors on mice result. Thus, on my extrapolation, a man can smoke over 50,000 cigarettes a day and not be in danger of developing cancer from smoking.

Extrapolations such as this show the dangers of predicting cancer-producing doses in man from mouse experience.

In his statement before this committee (Page 146) Wynder said he produced about 50 grams of tar per 1,000 cigarettes, or 50 milligrams per cigarette. This raises the question whether this tar was produced under conditions simulating human smoking, since
none of the figures presented to you Wednesday indicated that much tar content to be in the smoke of a cigarette.

4. Experimental projects carried out by Kotin and his associates at the University of Southern California in Los Angeles in exposing mice to Los Angeles atmosphere in natural and artificial forms show how potent the pollutants in air can be in the production of tumors.

Kotin and his group applied various substances that contribute to air pollution on a quantitative basis. Incidentally he used a lesser dosage in one year, weight for weight, than Wynder used in one week. When material obtained from diesel exhaust fumes was so applied, 17 out of 20 animals bore tumors, or 85%, and 11 of these 17 tumors were cancerous. When a similar experiment was conducted again with a pure strain of mice, using a concentrate from gasoline internal combustion engines, 38 out of 86 mice developed tumors; there were multiple tumors in over 60% of the animals and 44%, or 22 out of the 38 animals with tumors had cancerous tumors.

Finally, when products simply filtered out of Los Angeles air were similarly applied, 13 out of 35 mice, or 42% developed tumors, and 9 of these 13 animals showed malignant tumors on microscopic examination.

This makes obvious the fact that duplicating the Wynder type of experiment, not only with diesel and gasoline exhaust concentrates, but also with samples of Los Angeles atmosphere, produced considerably more convincing evidence of cancer-producing ability in mice, for what it may be worth, than did the Wynder experiment.

As a further note, it should be remarked that Kotin's observations have been duplicated readily by several other competent investigators, while Wynder's results have been difficult of reproduction by other scientists.

In summary, the total evidence here reviewed fails to establish any sound basis on which a causative influence may be assigned to cigarette smoking in the production of cancer of the lung. As in a majority of human cancers, we have at hand an imposing list of predisposing factors, none of which is of more than ephemeral status. The total problem of cancer in homo sapiens from the standpoint of its basic cause remains as much an impenetrable mystery as in the days of Aesclapius.