

REPRINTS AND REFLECTIONS

Smoking and lung cancer: recent evidence and a discussion of some questions*

Jerome Cornfield,¹ William Haenszel,² E. Cuyler Hammond,³ Abraham M. Lilienfeld,⁴ Michael B. Shimkin⁵ and Ernst L. Wynder⁶

Summary This report reviews some of the more recent epidemiologic and experimental findings on the relationship of tobacco smoking to lung cancer, and discusses some criticisms directed against the conclusion that tobacco smoking, especially cigarettes, has a causal role in the increase in broncho-genic carcinoma. The magnitude of the excess lung-cancer risk among cigarette smokers is so great that the results can not be interpreted as arising from an indirect association of cigarette smoking with some other agent or characteristic, since this hypothetical agent would have to be at least as strongly associated with lung cancer as cigarette use; no such agent has been found or suggested. The consistency of all the epidemiologic and experimental evidence also supports the conclusion of a causal relationship with cigarette smoking, while there are serious inconsistencies in reconciling the evidence with other hypotheses which have been advanced. Unquestionably there are areas where more research is necessary, and, of course, no single cause accounts for all lung cancer. The information already available, however, is sufficient for planning and activating public health measures.
– *J. Nat. Cancer Inst.* **22**:173–203, 1959.

In 1957 a Study Group¹, appointed by the National Cancer Institute, the National Heart Institute, the American Cancer Society, and the American Heart Association, examined the scientific evidence on the effects of tobacco smoking on health and arrived at the following conclusion:

“The sum total of scientific evidence establishes beyond reasonable doubt that cigarette smoking is a causative factor in the rapidly increasing incidence of human epidermoid carcinoma of the lung.”

Concurrently, a report from the Medical Research Council² of Great Britain appeared which also drew the inference of a causal relationship between smoking and lung cancer from the statistical, clinical, and laboratory evidence available by midyear 1957.

The consideration of the accumulated scientific evidence has led to the acceptance of a similar viewpoint by responsible public health officials in Great Britain, the Netherlands, Norway, and the United States. This consensus of scientific and public health opinion does not mean that all problems, regarding smoking and lung cancer have now been solved or that valid questions and reservations about some aspects of the subject do not remain. An excellent collection of

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¹ School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Md. Department of Biostatistics, paper #323.

² National Cancer Institute, Public Health Service, U.S. Department of Health, Education, and Welfare, Bethesda, Md.

³ American Cancer Society, Inc., New York, N.Y.

⁴ School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Md.

⁵ National Cancer Institute, Public Health Service, U.S. Department of Health, Education, and Welfare, Bethesda, Md.

⁶ Sloan-Kettering Institute for Cancer Research, New York, N.Y.

primary references and opinions expressing both "sides" of the question was issued by a committee of the House of Representatives³ which sought to examine the claims of filter-tip cigarette advertisements.

The general acceptance of the cigarette-lung-cancer relationship has not decreased research interest but has accelerated research in this and in such related fields as respiratory physiology and environmental carcinogens, and on the effect of tobacco smoke in a wide range of physiological and pathological reactions.

The result is that considerably more information has been published or has become available through other media. Included in the recent scientific evidence are the following:

- (1) Additional retrospective studies^{4,5,6} on men with lung cancer and on matched controls have appeared. All show an association between cigarette smoking and epidermoid-undifferentiated lung cancer.
- (2) Additional retrospective studies on women^{7,6} also show the association.
- (3) The first results of a third large prospective study⁸, which included 200,000 United States veterans who were observed for 30 months, duplicate closely the reported findings of the Hammond-Horn⁹ and the Doll-Hill¹⁰ studies.
- (4) Analyses by Kreyberg and others^{11,12} substantiate that, epidemiologically, primary lung cancer must be divided into epidermoid-undifferentiated and adenocarcinoma. The latter is much less related to smoking and, so far as is known at present, to other carcinogenic inhalants.
- (5) Additional findings have become available on the impingement of tobacco-smoke particles in the bronchi of animals, ciliary paralysis, and penetration of unidentified fluorescent materials into the bronchial cells.^{13,14,15}
- (6) Additional data have been published^{16,17} on the more frequent occurrence of hyperplastic and metaplastic changes in the lungs of smokers as compared with the lungs of nonsmokers. Hyperplastic and metaplastic changes have been produced in bronchi of dogs exposed to direct contact with tobacco "tars"¹⁸ and in bronchi of mice exposed to tobacco smoke.¹⁹
- (7) Additional confirmations have been obtained on the induction of cancer of the skin in mice painted with tobacco-smoke condensates.^{20,21,22,23,24}
- (8) Progress continues on the isolation and identification of chemical constituents in tobacco smoke, including compounds of the carcinogenic polycyclic type.^{25,25,26,27,28}

The growing and consistent body of evidence has had no noticeable effect upon the viewpoint of a small but important group of individuals who would

deny a causal role of cigarette smoking in cancer of the lung. Among these critics are Little²⁹ and Hartnett³⁰, spokesmen for the American tobacco industry. Berkson^{31,32} has been critical of many aspects of the statistical studies, and his reservations are, in part, also evident in papers by Neyman³³ and Arkin³⁴. More general objections by Fisher^{35,36}, Greene³⁷, Hueper³⁸, Macdonald³⁹, Rigdon⁴⁰, and Rosenblatt⁴¹ have been published.

We have reviewed the criticism that have been made regarding the cigarette-lung cancer relationship in the light of new evidence. In this review we have several objectives: a) to point out recorded facts that directly answer some of the criticisms; b) to define more precisely some inadequacies of information, with the hope that this will lead to further research. The particular references we have used were selected because in our opinion the criticism was well stated; it is not our intention to reply to any specific publication or to any specific critic. Our view is that all valid questions should be answered. However, some questions may not be relevant, or there may be no information presently available for an answer. In the latter case, we believe that a distinction should be made between data that are unavailable and data that have been found to be contradictory.

For convenience, we have divided the criticisms and answers into five major topics, as follows: (I) Mortality and population data; (II) Retrospective and prospective studies; (III) Studies on pathogenesis; (IV) Other laboratory investigations; and (V) Interpretation.

I. Mortality and Population Data

The rising death rate from lung cancer in all countries that have sufficiently detailed mortality statistics is the most striking neoplastic phenomenon of this century. That this increase is a fact and not a spurious result of statistical classification is now commonly accepted. An entirely contrary view is held by only a few persons⁴⁰, though there are dissenting opinions^{42,38} regarding the extent and time relationship of this recorded increase.

Obviously, the case for the etiologic role of cigarette smoking would be seriously compromised if it could be demonstrated that the lung-cancer rate over the past half century had been stationary, particularly after 1920 when much of the rise in cigarette consumption, instead of other forms of tobacco, occurred⁴³.

In a recent review, Rigdon and Kirchoff⁴⁴ document that primary lung cancer was first recognized as an entity during the early part of the 19th century, and that its occurrence has increased steadily since then, as manifested by the recorded relative frequency with which it was recognized in the clinic and at necropsy. This is undoubtedly correct but does not constitute evidence against a true increase in the incidence

of the disease during the whole, or a more recent part, of the last 100 years.

Hueper³⁸, accepting a true increase in the incidence of lung cancer, regards an increase dating back to 1900, or before the widespread use of cigarettes, as evidence against the cigarette-lung-cancer relationship. His contention would have crucial import only if it were maintained that cigarette smoking is the sole cause of lung cancer.

The vital statistics and the necropsy data that support the presumption of a real increase in lung-cancer risk certainly apply to the years after 1920. Because of the uncertainties associated with changes in diagnostic accuracy, no firm conclusions can be reached on whether the *rate* of increase in lung-cancer mortality has, in truth, accelerated since 1920.

Effect of Aging

Rosenblatt⁴¹ has raised the question about the effect of the aging population on the lung-cancer rate. This particular point has been investigated by the use of age-adjusted rates. Dunn⁴⁵ has noted that only one sixth of the over-all increase in lung-cancer mortality among males in the United States (from 4 to 24 deaths per 100,000 males between 1930 and 1951) could be attributed to an aging population. Similar findings⁴⁶ have been presented for England and Wales where observations on lung-cancer mortality date back to 1900; the 1953 mortality rate for both sexes, 34 per 100,000 population, was 43 times the corresponding 1900 rate, 0.8 per 100,000 population. Allowance for increased average age of the population could account for only half this rise in lung-cancer mortality, with a 24-fold difference between 1900 and 1953.

Also, an aging population, does not affect the age-specific death rates and cannot account for the phenomenon of increasingly higher lung-cancer mortality at all ages throughout the lifespan, which has occurred among successively younger groups of males born in the United States and England and Wales since 1850. A similar but less pronounced "cohort displacement" has been shown for females.

Diagnostic Factors

Little²⁹ and others⁴⁰ have raised the important question on whether better diagnostic measures and more complete reporting have resulted in a spurious increase in the recorded attack rate. Several special features of the increase in lung-cancer mortality would be difficult to account for on diagnostic grounds. These include the continuous rising ratio of male to female deaths, the increasing lung-cancer mortality rate among successively younger cohorts, and the magnitude of the current, continuing, increase in lung-cancer mortality⁴⁶. By 1955, among white males, 50 to 64 years of age, in the United States, more deaths were attributed to lung cancer than to all other respiratory diseases combined.

Gilliam⁴² has made a careful study of the potential effect of improved diagnosis on the course of the lung-cancer death rate. Even assuming that 2 percent of the deaths certified in past years as tuberculosis or other respiratory disease were really due to lung cancer, he concluded that "... all of the increase in mortality attributed to cancer of the lung since 1914 in United States white males and females cannot be accounted for by erroneous death certification to other respiratory diseases without unreasonable assumptions of age and sex differences in diagnostic error." His computations reduced the respective 26-fold and sevenfold increase in lung-cancer mortality among males and females, between 1914 and 1950, to the more modestly estimated dimensions of fourfold and 30 percent, respectively. These estimates are certainly the lower bound on the magnitude of the true rate of increase during this period.

The Copenhagen Tuberculosis Station data, examined by Clemmesen *et al.*⁴⁷, provide the greatest measure of control on the diagnostic improvement factor. In a tuberculosis referral service, used extensively by local physicians, where diagnostic standards and procedures including systematic bronchoscopy remained virtually unchanged between 1941 and 1950, the lung-cancer prevalence rate among male examinees increased at a rate comparable to that recorded by the Danish cancer registry for the total male population. This can be regarded as evidence that the reported increase in Danish incidence is not due to diagnostic changes.

Necropsy Data

Most necropsy data agree with mortality data on the increase in lung-cancer risk. To establish this point we referred to a necropsy series summarized by Steiner⁴⁸, and returned to the original sources for evidence on the nature of changes over time. Since an existing compilation was chosen, the results do not represent a culling of autopsy series for data favorable to this thesis. The findings from 13 series are summarized in text-figure 1 as the proportion of lung cancers in relation to all necropsies. The relative frequency in terms of total tumors or total carcinomas yielded results which would lead to substantially the same inferences.

Mortality and necropsy data have their own virtues and weaknesses. Death certificates provide a complete report of deaths, but do not emphasize a high quality of diagnostic evidence, while the reverse holds true for necropsies. However, since both approaches lead to the same inferences, neither great variation in the quality of diagnostic evidence nor the unrepresentative nature of some of the necropsy observations can be viewed as plausible interpretations of the results. The alternative conclusion of a real increase in lung-cancer risk remains.

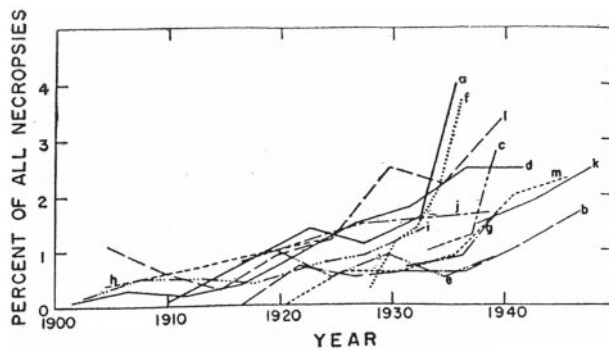


Figure 1

Urban-Rural Differences

Emphasis has been placed on the alleged incompatibility of the excess lung-cancer mortality, among urban residents, with the cigarette-smoking hypothesis^{38,49}. Mortality data from several countries indicate strongly that lung-cancer rates are much higher in cities than in rural areas, and the observation that urban males in general have higher lung-cancer mortality than rural males is undoubtedly correct.

The assertion of Macdonald³⁹ that "...country people smoke as much, if not more, than do city people ..." is not borne out by the facts⁵⁰. Nevertheless, the evidence indicates that adjustment for smoking history could account for only a fraction of this urban-rural difference⁵¹.

However, this does not establish the converse proposition that control of residence history in the analysis of collected data would account for the excess lung-cancer risk among cigarette smokers. Evidence now in hand weighs strongly against this last assertion. Stocks and Campbell⁶⁷, in their report on lung-cancer mortality among persons in Liverpool, the suburban environs, and rural towns in North Wales, showed that heavy smokers have higher lung-cancer rates when urban and rural males were studied separately. Mills and Porter⁵² reported similar findings in Ohio. These results agree with the experience of the Hammond-Horn⁹ study, which revealed markedly higher death rates for bronchogenic carcinoma among smokers regardless of whether they lived in cities or in rural areas. No contradictory observations are known to us.

Sex Differences

The sex disparity in lung-cancer mortality has also been cited^{35,7} as grounds for discarding the cigarette-smoking hypothesis. In this connection it should be noted that persons advocating this line of argument have minimized sex differences in smoking habits to a degree not supported by available facts. A survey of smoking habits in a cross section of the United States population⁵⁰ demonstrated that men, on the average, have been smoking for longer periods than women. The sex differences in tobacco use were

especially pronounced at ages over 55, when most lung-cancer deaths occur; 0.6 percent of United States females in this age group have been reported as current users of more than 1 pack of cigarettes daily compared to 6.9 percent of United States males. British data⁵³ also revealed much lower tobacco consumption among females, particularly for the years before World War II.

The present data contrasting the experience by sex would appear to support the cigarette-smoking hypothesis rather than discredit it. When differences in smoking habits are considered, it is possible to reduce the observed fivefold excess lung-cancer mortality among males to the 40 percent excess mortality which prevails for many other causes of death⁵¹. One intriguing finding from these studies is that the estimated death rates for female nonsmokers agree closely with the death rates derived from retrospective studies on male nonsmokers⁷.

Evidence for Other Etiological Factors

Etiologic factors of industrial origin, such as exposure to chromates and coal gas, are well established⁴⁶. Excess lung-cancer risks among such groups as asbestos workers who develop asbestosis, appear likely⁴⁶. One epidemiologic study⁵⁴ of British, World War I, veterans exposed to mustard gas and/or with a wartime history of influenza revealed virtually no excess lung-cancer risk among these groups.

The existence of other important lung-cancer effects associated with such characteristics as socioeconomic class cannot be questioned. Cohart⁵⁵ found that the poorest economic class had a 40 percent higher lung-cancer incidence than the remaining population of New Haven, Connecticut. Results from the 10-city morbidity survey⁵⁶ have revealed a sharp gradient in lung-cancer incidence, by income class, for white males, which is consistent with Cohart's findings. Since cigarette smoking is not inversely related to socioeconomic status, we can agree with Cohart "... that important environmental factors other than cigarette smoking exist that contribute to the causation of lung cancer." These and other findings are convincing evidence for multiple causes of lung cancer. It is obviously untenable to regard smoking of tobacco as the sole cause of lung cancer.

Two points should be made: The population exposed to established industrial carcinogens is small, and these agents cannot account for the increasing lung-cancer risk in the remainder of the population. Also, the effects associated with socioeconomic class and related characteristics are smaller than those noted for smoking history, and the smoking-class differences cannot be accounted for in terms of these other effects.

Special population Groups

Haag and Hanmer⁵⁷ reported that employees in 9 processing plants of the American Tobacco Company,

with an above-average proportion of smokers, had a lower mortality than the general population of Virginia and North Carolina for all causes and for cancer and cardiovascular diseases, but no higher mortality for respiratory cancer and coronary disease. They concluded: "The existence of such a population makes it evident that cigarette smoking *per se* is not necessarily or invariably associated with a higher risk of lung cancer or cardiovascular diseases or with diminished longevity."

The group studied by Haag and Hanmer was too small to yield significant results on respiratory cancer. Moreover, a major flaw in the conclusion has been pointed out by Case⁵⁸. It is well known that mortality comparisons cannot be drawn directly between employee groups and the general population, since the death rates for many groups of employed persons are lower than death rates for the general population with age, sex, and race taken into consideration. This is true because there is a strong tendency to exclude from employment those persons who have acute or chronic diseases or who are seriously disabled from any cause and those employees who develop permanent disabilities from disease or other causes are usually discharged, retired, or dropped from the list of regular employees. Reasons of this nature undoubtedly account for the deficit in deaths from all causes noted in the group of employees under consideration.

A different picture is provided by the Society of Actuaries⁵⁹ who made a study for 1946 through 1954. The death claims for employees of the tobacco industry were reported to be slightly higher than, and the permanent disability claims were reported to be over three times as high as, those for employees in nonrated industries as a whole. This latter comparison indicates that the basic assumption of the Haag and Hanmer study is incorrect. Also, interpretation of group comparisons in this field should account separately for the experience of smokers and nonsmokers. We hope that Haag and Hanmer will supplement the report to provide data for smokers and nonsmokers in the study population.

II. Retrospective and Prospective Studies

The association between smoking and lung cancer has now been investigated and reported by at least 21 independent groups of investigators in 8 different countries, who employed what is known as the retrospective method^{1,4,5,6,7,46}. In these studies, patients with lung cancer, or their relatives, were questioned about their smoking history and other past events, and the answers compared with those of individuals without lung cancer who were selected as controls. Although these 21 studies have certain features in common, they varied greatly in the methods of

selecting the groups, the methods of interview, and other important aspects.

The association between smoking and lung cancer was further investigated in two countries by three independent groups^{8,9,10}, using the prospective method. In these studies, large groups were questioned on smoking habits and other characteristics, and the groups were observed for several years for data on mortality and causes of death. The three prospective studies also varied in several important details including the type of subjects, the selection of subjects, and the method of obtaining information on smoking habits.

In each of these studies, an association was found between smoking and lung cancer. In every investigation where the type of smoking and lung cancer. In every investigation where the type of smoking was considered, a higher degree of association was found between lung cancer and cigarette smoking than between lung cancer and pipe or cigar smoking. In every instance where amount of smoking was considered, it was found that the degree of association with lung cancer increased as the amount of smoking increased. When ex-cigarette smokers were compared with current cigarette smokers, it was found that lung-cancer death rates were higher among current cigarette smokers than among ex-cigarette smokers.

A number of investigators⁶⁰ have criticized the retrospective method but, for the most part, the specific points of criticism apply only to some of the studies and not to others. Some features of the three prospective studies on smoking also have been criticized. Again, certain of the points of criticism apply to one or another of the three prospective studies but not to all three. Specifically, doubts raised as to the validity of the early findings of the prospective studies have been eliminated by the persistence of the findings in the later phases of the same studies.

The validity of the findings on these extensive investigations has been questioned in regard to two major aspects: 1) the methods of selection of the study groups, and 2) the accuracy of information regarding smoking habits and the diagnosis of lung cancer.

Selection of Study Groups

Neyman³³ pointed out that a study based on a survey of a population at some given instant of time may yield misleading results. Suppose that a study is made on a day when all patients with lung cancer and a group of people without lung cancer are questioned about their smoking habits. If smokers with lung cancer live longer than nonsmokers with lung cancer, there would be a higher proportion of smokers in the lung-cancer group than in the control group – this would follow without questioning the proposition on which the model is based. However, only two of the retrospective studies were conducted in a way approximating an "instantaneous survey" procedure, so that this criticism does not apply to most of the

studies. Furthermore, this difficulty is completely avoided in prospective studies.

Berkson³¹ indicated that people with two specific complaints are more likely to be hospitalized than people with only one of these complaints. If a retrospective study were conducted exclusively on hospital patients an association would be found between these two specific complaints, even if there were no association between the same two complaints in the general population. This would influence the results if smokers with lung cancer are more likely to be hospitalized than nonsmokers with lung cancer. However, Berkson showed that this difficulty is trivial if a high percentage of people with either one of these two conditions is hospitalized, which is the situation with lung-cancer patients. Furthermore, one retrospective study⁶⁷ included all lung cancer patients who were in the study area, including those not hospitalized; another retrospective study⁶¹ was based on individuals who died of lung cancer and other diseases regardless of whether they had been hospitalized or not. This difficulty does not arise in prospective studies.

In all but one of the 21 retrospective studies, the procedure was to compare the smoking habits of lung-cancer patients with the smoking habits of a control group who did not have lung cancer. Hammond⁶⁰, Berkson³¹, and others have pointed out the grave danger of bias if the control group is not selected in such a way as to represent (in respect to smoking habits) the general population which includes the lung-cancer patients. Subsequent events have proved that this criticism is well founded, though the direction of the bias in most studies turned out to yield an underestimate of the degree of association between cigarette smoking and lung cancer. The reason was that in most of the retrospective studies the control group consisted of patients with diseases other than lung cancer. The choice of such a control group is tantamount to assuming that there is no association between smoking and diseases which resulted in hospitalization of the control subjects. This was an incorrect assumption since other studies have indicated an association between smoking and a number of diseases, such as coronary artery disease, thromboangiitis obliterans, and cancer of the buccal cavity.

Doll and Hill⁶², recognizing the possibility of bias in a control group selected from hospital patients, obtained an additional control group by ascertaining the smoking habits of the general population in a random sample of the area in which their hospital was located. The largest percentage of smokers (particularly heavy smokers) was found in the lung-cancer group, the smallest percentage of smokers was found in the general population sample, and an intermediate percentage of smokers was found in the hospital-control group. Similar results have been reported in a recent study of women⁷.

Berkson³¹ pointed out that the criticisms in regard to selection bias in the retrospective studies are also applicable to the earlier findings in a prospective study. Suppose that, in selecting subjects for a prospective study, sick smokers are overrepresented in relation to well smokers and/or well non-smokers are overrepresented in relation to sick nonsmokers. In this event, during the earlier period after selection, the death rate of the smokers in the study would be higher than the death rate of the nonsmokers in the study, even if death rates were unrelated to smoking habits of the general population. If smoking is unrelated to death from lung cancer (or other causes), the death rate of the smokers would tend to equalize with that of the nonsmokers as the study progressed. Thus, the bias would diminish with time, and a relationship due to such bias would disappear. This general principle is well known to actuaries and is one of the cornerstones of the life insurance business.

Hammond and Horn⁹, recognizing this possible difficulty, excluded from the study all persons who were obviously ill at the time of selection. As expected, the total death rate of the study population was low and very few deaths from lung cancer occurred during the first 8 months after selection. The total death rate, and particularly the death rate from lung cancer, rose considerably in the subsequent 3 years. What is more important, the observed association between cigarette smoking and lung cancer was considerably higher in the latter part than in the early part of the study, and the association between cigarette smoking and total death rates was also somewhat greater in the latter part of the study. This showed that the original bias in the selection of the subjects was slight and that it yielded an underestimate of the degree of association between smoking and death rates.

This particular problem was not encountered in the prospective studies of Doll and Hill¹⁰ who could observe the death rates of all physicians in Great Britain (nonresponders as well as responders to the smoking questionnaire). The prospective study of Dorn⁸ also had a defined population of veterans holding insurance policies, and nonresponders were observed as well as responders. Moreover, these two studies also showed that higher mortality from lung cancer among smokers was more evident during the later period than in the earlier period of observation. Thus, in the course of time, there was no disappearance of any selection bias factors that may have been introduced into the original study groups.

The subjects for the Hammond and Horn prospective study⁹ were selected by volunteer workers with specific instructions on how it should be done. Mainland and Herrera⁶³ have suggested that the volunteer workers may have introduced a bias in the way they selected the subjects. The foregoing evidence of persistence and accentuation of the differences between smokers and nonsmokers, in time, effectively counters

purposeful, as well as unknown, sources of such selection.

Accuracy of Information

Berkson^{31,32} has remarked that the two major variables considered in all these studies – the ascertainment of smoking habits and the diagnosis of disease – are both subject to considerable error. The accuracy of diagnosis is not a major problem in retrospective studies because the investigator can restrict his study to those patients whose diagnosis of lung cancer has been thoroughly confirmed. This feature has been taken into consideration in several retrospective studies. It is more of a problem in prospective studies since all deaths that occur must be included, and certainly some of the diagnoses will be uncertain. However, in all three prospective studies, the *total death rate* was found to be higher in cigarette smokers than in nonsmokers and found to increase with the amount of cigarette smoking. If some of the excess deaths associated with cigarette smoking and ascribed to lung cancer were actually due to some other disease, then it means that: a) the association between cigarette smoking and lung cancer was somewhat overestimated, but b) the association between smoking and some other disease was somewhat underestimated. The reverse would be true if some of the excess deaths associated with cigarette smoking and ascribed to diseases other than lung cancer were actually due to lung cancer. Hammond and Horn⁹ found that the association with cigarette smoking was greater for patients with a well-established diagnosis of lung cancer than for patients with less convincing evidence for a diagnosis of lung cancer. This suggests that inaccuracies in diagnosis resulted somewhat in an underestimate of the degree of association between smoking and lung cancer.

The study on physicians, by Doll and Hill¹⁰, in which presumably the clinical and pathologic evidence of the cause of death would be somewhat more than in the general population considered by Hammond and Horn and by Dorn, yields almost identical risks to lung cancer by smoking class.

In regard to information about smoking, Finkner *et al.*⁶⁴ have made a thorough study of the accuracy of replies to questionnaires on smoking habits. Their results indicate that replies are not completely accurate but that most of the errors are relatively minor – very few heavy smokers are classified as light smokers. Random and independent errors simply tend to diminish the apparent degree of association between two variables. A national survey of smoking habits in the United States⁵⁰ yielded results on tobacco consumption that were consistent with figures on tobacco production and taxation.

On two occasions several years apart, Hammond and Horn⁹ and Dorn⁸ questioned a proportion of their subjects. The results indicated close reproducibility in the answers.

Hammond⁶⁰ and others³⁹ have questioned the reliability of the retrospective method on the grounds that the illness may bias the responses given by the patient or his family when they are questioned about smoking habits, and that knowledge of the diagnosis may bias the interviewer. This possible difficulty was minimized in several of the 21 retrospective studies on smoking in relation to lung cancer. For example, in the study conducted by Levin⁶⁵, all patients admitted to a hospital during the course of several years were questioned about their smoking habits *before* a diagnosis was made. Only a small proportion later turned out to have lung cancer, though many had lung disease symptoms or lung diseases other than lung cancer. Doll and Hill¹⁰ also showed that patients whose diagnosis of lung cancer was subsequently established to be erroneous had smoking histories characteristic of the control rather than of the lung-cancer group. Furthermore, a larger percentage of cigarette smokers have been found among patients with epidermoid carcinoma of the lungs than among patients with adenocarcinoma of the lungs⁶⁶. This could hardly have resulted from bias either on the part of the patient or on the part of the interviewer.

Multiple Variables

Arkin³⁴, Little²⁹, Macdonald³⁹, and others have criticized the studies of cigarette-lung cancer relationship on the grounds that only smoking habits were really investigated, and that numerous other possible variables were not considered.

This criticism may seem especially appropriate in view of the accepted fact that no single etiologic factor has been proposed for any neoplastic disease. The criticism may also be valid in relation to any one of the retrospective and prospective studies. However, in the aggregate, quite a number of other variables have been specifically investigated or can be inferentially derived. Of course, all studies considered the basic factors of age and sex; some dealt with geographic distribution⁶⁷, occupation⁶⁸, urban or rural residence⁶⁷, marital and parous status⁷, and some other habits such as coffee consumption⁷.

The Doll and Hill¹⁰ prospective study was confined to a single professional group, physicians. Thus there could be no great variation attributable to occupation or socioeconomic status. Stocks and Campbell⁶⁷ put particular emphasis on the study of air pollution and occupational exposure and included a number of other factors in addition to smoking. It is evident, in the Hammond-Horn⁹ study and other investigations, that there is a consistent relationship between urban residence and a higher mortality due to lung cancer. The important fact is that in all studies, when other variables are held constant, cigarette smoking retains its high association with lung cancer.

The only factors that may show a higher correlation with lung cancer than heavy cigarette smoking are such occupations as those of the Schneeberg miners

and manufacturers of chromate⁴⁶. We are not acquainted with actual studies of these and related occupation groups in which cigarette and other tobacco consumption is also considered. Such studies, we suggest, would be useful additions to our knowledge of other etiologic agents of the interplay between multiple causes in human pulmonary cancer.

III. Studies on Pathogenesis

Inhalation of Smoke

If cigarette smoking produces cancer of the lungs as a result of direct contact between tobacco smoke and the bronchial mucosa, smokers who inhale cigarette smoke should be exposed to higher concentrations of the carcinogens than noninhalers and therefore have a higher risk to the development of lung cancer. The retrospective study of Doll and Hill⁶², however, elicited no difference between patients with lung cancer and the controls in the proportion of smokers who stated that they inhaled. Fisher³⁵, Hueper³⁸, and Macdonald³⁹ have emphasized this point as contradictory to the smoking-lung-cancer relationship, and, of course, it is. Unfortunately, this particular finding was not reinvestigated in the prospective study of Doll and Hill¹⁰.

Three authors, Lickint⁶⁹, Breslow *et al.*⁶⁸, and Schwartz and Denoix⁴, however, *did* find the relative risk of lung cancer to be greater among inhalers than among noninhalers when age, type, and amount of smoking were held constant. It must be admitted that there is no clear explanation of the contradiction posed by the Doll-Hill⁶² findings, though a number of plausible hypotheses could be advanced. More experimental work is required, including some objective definition and measurement of the depth and length of inhalation.

Hammond⁷⁰ has recently queried male smokers about their inhalation practices. He found that very few pipe and cigar smokers inhale; that most men inhale who smoke only cigarettes; and that there are proportionally fewer inhalers among men who smoke both cigars and cigarettes than among men who smoke only cigarettes. These findings are compatible with the view that differences in inhaling account for the fact that the lung-cancer death rate of cigar and pipe smokers is less than the lung-cancer death rate of cigarette smokers; and that the lung-cancer death rate of men who smoke both cigars and cigarettes is somewhat lower than the lung-cancer death rate of men who smoke only cigarettes.

Upper-Respiratory Cancer

Rosenblatt⁴¹ has drawn attention to the fact that increased consumption of cigarettes has not been accompanied by an increase in upper-respiratory cancer similar to that noted in cancer of the lung and bronchus. Hueper³⁸ also has expressed doubts

about the causative role of cigarette smoking on the basis that cigarette smoking is not associated with cancer of the oral cavity or of the fingers, which are often stained with tobacco tar.

The premise that a carcinogen should act equally on different tissues is not supported by experimental or clinical evidence⁷¹. Carcinogens, which produce liver tumors in animals, may be noncarcinogenic when applied to the skin. Coal soot, accepted as etiologically related to carcinoma of the scrotum in chimney sweeps, does not increase the risk to cancer of the penis. There is no *a priori* reason why a carcinogen that produces bronchogenic cancer in man should also produce neoplastic changes in the nasopharynx or in other sites. It is an intriguing fact, deserving further research, that carcinoma of the trachea is a rarity, whereas carcinoma of the bronchus is common among individuals exposed to chromates, as well as among chronic cigarette smokers.

Several studies have established the association of all types of tobacco smoking, including cigarettes, with cancer of the oral cavity⁷². However, the *relative* risk of developing cancer of the mouth is greater for cigar and pipe smokers than for cigarette smokers. The risk of laryngeal cancer is increased by smoking and an equal risk exists among cigarette, cigar, and pipe smokers⁷³. The per capita consumption of cigars and pipe tobacco has decreased since 1920, while cigarette smoking has increased⁴³.

These associations contrast sharply with the findings on lung cancer, which have consistently shown that cigarette smokers have much higher risks than either cigar or pipe smokers. Since 1920 the increase in tobacco consumption has been primarily due to the rise in cigarette consumption⁴³, and the stabler rates for intra-oral and laryngeal cancer, while the lung-cancer rates have increased steeply, can be considered compatible with the causal role of cigarette smoking in lung cancer.

Effect of Tobacco Smoke on Bronchial Mucosa

Statements by Hartnett³⁰, Macdonald³⁹, and others^{31,29} imply that the relationship of cigarette smoking and lung cancer is based exclusively on "statistics" and lacks "experimental" evidence. The differentiation between various methods of scientific inquiry escapes us as being a valid basis for the acceptance or the rejection of facts. Nevertheless it is true that historically the retrospective studies on lung cancer preceded the intensive interest in laboratory investigations stimulated by the statistical findings.

Hilding¹³ has shown experimentally that exposure to cigarette smoke inhibited ciliary action in the isolated bronchial epithelium of cows. Kotin and Falk¹⁵ obtained essentially the same results in experiments on rats and rabbits. Hilding¹⁴ further showed that inhibition of ciliary action interfered with the mechanism whereby foreign material is ordinarily removed

from the surface of bronchial epithelium. In addition, he found that foreign material deposited on the surface tended to accumulate in any area where the cilia have been destroyed. Auerbach *et al.*¹⁶ found that the small areas of the bronchial epithelium where ciliated columnar cells were absent appeared more frequently in smokers than in nonsmokers. Chang¹⁷ found that cilia were shorter, on an average, in the bronchial epithelium of smokers than in that of nonsmokers.

These studies have demonstrated the existence of a mechanism whereby foreign material from any source (e.g. tobacco smoke, industrial dusts, fumes from automobile exhausts, general air pollutants, and, perhaps, pathogenic organisms) is likely to remain in contact with the bronchial epithelium for a longer period in smokers than in nonsmokers.

Auerbach and his associates¹⁶ studied the microscopic appearance of the bronchial epithelium of patients who died of lung cancer and patients who died of other diseases. Each of these two groups of patients was classified according to whether they were nonsmokers, light smokers, or heavy cigarette smokers. Among the cancer patients there were no nonsmokers. Approximately 208 sections from all parts of the tracheobronchial tree from each patient were examined. Many areas of basal cell hyperplasia, squamous metaplasia, and marked atypism, with loss of columnar epithelium were found in the tracheobronchial tree of men who had died of lung cancer. Almost as many such lesions were found in heavy cigarette smokers who had died of other diseases; somewhat less were found in light cigarette smokers; and much less in nonsmokers. Chang¹⁷ has reported similar findings in the bronchial epithelium of smokers compared with nonsmokers.

The chief criticism of Auerbach's study has concerned terminology. Following the definition previously set forth by Black and Ackerman⁷⁴, Auerbach *et al.* used the term "carcinoma-*in-situ*" to describe certain lesions with marked atypical changes and loss of columnar epithelium. Whether this is an appropriate term may be questioned, but it is not relevant to the validity of the findings. Certainly there are no data to indicate what proportion of these morphologically abnormal areas would progress to invasive carcinoma.

The recent findings of Auerbach *et al.* and Chang have been reproduced experimentally in animals. Rockey and his associates⁷⁵ applied tobacco "tar" directly to the bronchial mucosa of dogs. Within 3 to 6 weeks, the tar-treated surface became granular and later developed wart like elevations. Upon microscopic examination, hyperplasia, transitional metaplasia, and squamous metaplasia were found in these areas. Leuchtenberger *et al.*¹⁹ exposed mice to cigarette smoke for periods up to 200 days. The bronchial epithelium was then examined microscopically. Bronchitis, basal-cell hyperplasia, and atypical basal-cell hyperplasia were found in the majority of

the animals and squamous metaplasia in a few. Further work and longer periods of observation are necessary to establish whether some of these lesions would progress to frank neoplasia.

IV. Other laboratory Investigations

Skin Cancer in Rodents

One of the links in the total evidence for the causal relationship of cigarette smoking and lung cancer is the demonstration that tobacco smoke condensates (usually referred to as "tars") have the biologic property of evoking carcinoma in certain laboratory animals, particularly mice. The production of skin cancer in mice, following repeated, long-term applications of tobacco tar, has now been reported from at least six different laboratories^{20,21,22,23,24,76}. It is undeniable that some investigators did not obtain positive results, perhaps because the dose and other experimental conditions were different, or because the complex tobacco tars probably varied widely in their composition. The negative results of Passey *et al.*¹⁸ have been quoted by Hueper³⁸ and others, but a more recent experiment by Passey²⁴ with Swiss strain mice did lead to the appearance of at least two carcinomas after repeated applications of tobacco-smoke condensate.

Little²⁹ indicated that "... the extrapolation to the human lung of results obtained by painting of or injection into the skin of mice is decidedly questionable". Direct extrapolation from one species to another is, of course, not justified. Nevertheless, results in animals are fully consistent with the epidemiologic findings in man. A quotation from Kotin⁴⁹ is appropriate: "The chemical demonstration of carcinogenic agents in the environment and their successful use for the production of tumours in experimental animals do not prove or even especially strongly suggest a like relationship in the instance of man. When, however, a demonstrable parallelism exists between epidemiologic data and laboratory findings, greater significance accrues to both. Medical history is replete with examples in which laboratory findings have been proved ultimately to have their counterpart in the human experience. Exceptions have been very few."

Greene³⁷, while discounting the significance of the induction of skin carcinoma in Swiss mice because of the constitutionally "high differential susceptibility" of the strain, believes that the failure to induce neoplasms in embryonic transplants exposed to tobacco tar is more important evidence. Greene's interesting technique does produce positive results when pure chemicals such as benzo[α]pyrene are used, and this chemical has been recovered from some samples of tobacco-smoke condensate. We are not acquainted with reports of neoplasms arising in embryonic tissue that has been exposed *in vitro* to coal tar, another crude mixture that contains carcinogens.

The high frequency of carcinoma induction reported by Wynder *et al.*⁷⁶ has not been achieved by other investigators, who reported that no more than 20 percent of animals, and usually considerably less, developed carcinoma of the skin. The presence of cocarcinogenic materials in tobacco-smoke condensates has been demonstrated by Gellhorn²² and by Bock and Moore²⁰. To the mouse data are now added the data on the induction of skin cancer in some rabbits painted with tobacco-smoke condensate⁷⁷; this condensate, when combined with a killed suspension of tubercle bacilli, and introduced into a bronchus, produced a carcinoma of the bronchus in one rat⁷⁸.

Since malignant neoplasms have been obtained in several strains of mice, and a few neoplasms have been produced in rabbits and rats, the issue of strain or species limitation to the reaction is more difficult to maintain. It is, of course, a fact that many agents shown to be carcinogenic to the skin of mice have not been proved carcinogenic to man. In most instances there is simply no experience with such agents in man, so that lack of proof really represents lack of data, pro and con.

The Problem of Dosage

Little²⁹ has further questioned the applicability of animal data to man, as follows: "Tobacco smoke or smoke condensate has failed to produce cancer even on the skin of susceptible strains of mice when applied in the quantity and at an exposure rate that would simulate conditions of human smoking."

The differences in species, tissues, and conditions between the induction of neoplasms on the skin of mice and in the bronchi of man, preclude fine comparisons of dose and time relationships.

Bronchogenic Cancer in Animals

The pulmonary adenomatous tumor in mice, rats, and guinea pigs cannot be compared with the bronchogenic carcinoma in man⁷¹. Until a few years ago, the experimental induction of epidermoid carcinoma had been achieved only in a few mice by passing strings impregnated with carcinogenic hydrocarbons through the lung. Epidermoid carcinoma of the lung was consistently produced in rats by beryllium⁷⁹, by carcinogenic hydrocarbons introduced as fixed pellets into bronchi of rats⁸⁰, and by inhalation of radioactive particles⁸¹.

Little²⁹ has noted that "... prolonged exposure of the lungs of rodents to massive doses of cigarette smoke has failed to produce bronchogenic cancer." This remains true at the time of this report, although it can be questioned whether any animal receives as large a dose of cigarette smoke through indirect exposure as a human being does by voluntary deep inhalation. Therefore the failure may be a technical one, which may be solved by further experimentation.

The early results of Leuchtenberger *et al.*¹⁹ suggested that this may be achieved.

Carcinogens in Tobacco Smoke

The isolation and identification of specific chemical constituents in tobacco smoke, which are carcinogenic for the pulmonary tissue of man, is an important area for research.

It has been clear for some time that combustion or pyrolysis of most organic material, including tobacco, will form higher aromatic polycyclics of established carcinogenic activity²⁸. A number of higher aromatic polycyclics have been identified and isolated (^{23,25,26,27}). These materials include benzo[*e*]pyrene, benzo[*a*]pyrene, dibenz[*a,h*]anthracene, chrysene, and, most recently, a newly established carcinogen, 3,4-benz-fluoranthene. Whether these compounds are equally involved in human pulmonary carcinogenesis is, of course, conjectural.

Little²⁹ has implied that a specific constituent must be found to account for the biologic activity of tobacco smoke. This is not necessary. The situation is similar to the establishment of the carcinogenic activity of tar, which was accepted before the isolation of benzo[*a*]pyrene by Kennaway and his coworkers. In this instance, also, benzo[*a*]pyrene is most probably not the only carcinogen in the complex mixture called tar, and there are strong indications that some noncarcinogenic components in tar may have cocarcinogenic effects.

V. Interpretation

Three interpretations of the observed association of lung cancer and cigarette smoking are possible: 1) that cigarette smoking "causes" lung cancer, either (a) through the direct carcinogenic action of smoke on human bronchial epithelium or (b) by a more indirect mode of action such as making the individual susceptible to some other specific carcinogenic agent in the environment; 2) that lung cancer "causes" cigarette smoking, perhaps because a pre-cancerous condition sets up a process which leads to a craving for tobacco; 3) that cigarette smoking and lung cancer both have a common cause, usually specified as a special constitutional make-up, perhaps genetic in origin, which predisposes certain individuals to lung cancer and also makes them cigarette smokers.

The second hypothesis was advanced by Fisher³⁶, apparently for the sake of logical completeness, and it is not clear whether it is intended to be regarded as a serious possibility. Since we know of no evidence to support the view that the bronchogenic carcinoma diagnosed after age 50 began before age 18, the median age at which cigarette smokers begin smoking, we shall not discuss it further.

The Constitutional Hypothesis

The first hypothesis may be referred to as the *causal* hypothesis and the third as the *constitutional* hypothesis. Nothing short of a series of independently conducted, controlled, experiments on human subjects, continued for 30 to 60 years, could provide a clear-cut and unequivocal choice between them. We nevertheless argue that evidence, in addition to that associating an increased mortality from lung cancer with cigarette smoking, is entirely consistent with the causal hypothesis but inconsistent, in many respects, with the constitutional hypothesis, so that even in the absence of controlled experimentation on human beings the weight of the evidence is for the one and against the other.

The difficulties with the constitutional hypothesis include the following considerations: (a) changes in lung-cancer mortality over the last half century; (b) the carcinogenicity of tobacco tars for experimental animals; (c) the existence of a large effect from pipe and cigar tobacco on cancer of the buccal cavity and larynx but not on cancer of the lung; (d) the reduced lung-cancer mortality among discontinued cigarette smokers. No one of these considerations is perhaps sufficient by itself to counter the constitutional hypothesis *ad hoc* modification of which can accommodate each additional piece of evidence. A point is reached, however, when a continuously modified hypothesis becomes difficult to entertain seriously.

Changes in Mortality

Mortality from lung cancer has increased continuously in the last 50 years, and considerably more for males than females. Such an increase can be explained either as the result of an environmental change (to which males are more exposed or more sensitive than females, if both are equally exposed) or as the result of a sex-linked mutation. The constitutional hypothesis must be modified in the light of this increase, since an unchanging constitutional make-up cannot by itself explain an increase in mortality. Proponents of the constitutional hypothesis have not indicated the type of modification they would consider. Three suggest themselves to us: 1) differences in constitutional make-up are genetic in origin, but rather than predisposing one to lung cancer, they make one sensitive to some new environmental agent (other than tobacco), which does induce lung cancer; 2) differences in constitutional make-up are not genetic but are the result of differential exposure to some new environmental agent, which both predisposes to lung cancer and creates a craving for cigarette smoke; 3) the mutation has led to a greater susceptibility to lung cancer and a preference for cigarette smoke.

In the first two situations the effect of the postulated constitutional make-up would be mediated through an environmental agent. The modified

hypothesis thus requires the existence of an environmental agent other than tobacco, exposure to which would be at least as highly correlated with lung-cancer mortality as exposure to cigarettes, and which also would be highly correlated with cigarette consumption. No such agent has yet been found or even suggested. In view of the magnitude of the increase in mortality from lung cancer, the third situation would require a mutation rate exceeding anything previously observed.

Experimental Carcinogenesis With Tobacco Tar

Condensed tobacco smoke contains substances that are carcinogenic for mouse and rabbit skin. It does not necessarily follow that these substances are also carcinogenic for human lungs nor does it follow that they are not. However, the constitutional hypothesis asserts they are not; and that it is simply a coincidence that these materials which are carcinogenic for experimental animals are also associated with a higher lung-cancer mortality in man.

Types of Tobacco and Cancer Site

A greatly increased lung-cancer risk is associated with increased cigarette consumption but not with increased consumption of pipe and cigar tobacco. Studies on cancer of the buccal cavity and larynx, however, have demonstrated a considerably higher risk among smokers, irrespective of the form or tobacco used. Only two ways of modifying the constitutional hypothesis to take account of this evidence occur to us: 1) There are two different constitutional make-ups, one of which predisposes to cigarettes but not to pipe and cigar consumption and to cancer of the lung, and the other predisposes to cancer of the buccal cavity and larynx but not of the lung and to tobacco consumption in any form. 2) Constitutional make-up predisposes to cigarette consumption and lung cancer only, but tobacco smoke, whether from cigarettes, cigars, or pipes, is carcinogenic for the mucosa of the buccal cavity and the larynx but not for the bronchial epithelium.

Mortality Among Discontinued Smokers

Mortality from lung cancer among discontinued cigarette smokers is less than that among those continuing to smoke^{9,10}; the magnitude of the reduction depending on amount previously smoked and the length of the discontinuance. The hypothetical constitutional factor which predisposes to lung cancer and cigarette smoking cannot therefore be a constant characteristic of an individual over his lifetime but must decrease in force at some time in life, thus resulting in the cessation of cigarette smoking and a concomitant, but not causally related, reduction in the lung-cancer risk. Furthermore, since cigarette smoking is rarely begun after age 35⁵⁰, it must be

inferred that the constitutional factor cannot increase in force with the passage of time, even though it may decrease.

In summary, the constitutional hypothesis does not provide a satisfactory explanation of all the evidence. It is natural, therefore, to inquire about the positive findings which support it. Even those who regard this hypothesis with favor would agree, we believe, that supporting evidence is quite scanty.

There are a number of characteristics in which cigarette smokers are known to differ from nonsmokers and presumably more will be discovered. Thus, cigarette smokers consume more alcohol, more black coffee, change jobs more often, engage more in athletics, and are more likely to have had at least one parent with hypertension or coronary artery disease⁸². Discontinued cigarette smokers are weaned at a later age than those continuing to smoke⁸³. Recently, Fisher⁸³ reported that 51 monozygotic twins resembled each other more in their smoking habits than 33 dizygotic twins, thus suggesting a genetic determinant.

Two somewhat obvious, but necessary, comments on results of this type are in order: 1) The demonstration that a characteristic is related to smoking status does not by itself create a presumption that it is a common cause. It must also be shown to be related to the development of lung cancer among subgroups of individuals with the same smoking status. Alcohol and coffee fail to meet this test, while none of the other characteristics related to smoking status have been investigated from this point of view. 2) There is a quantitative question. Cigarette smokers have a ninefold greater risk of developing lung cancer than nonsmokers, while over-two-pack-a-day smokers have at least a 60-fold greater risk. Any characteristic proposed as a measure of the postulated cause common to both smoking status and lung-cancer risk must therefore be at least nine-fold more prevalent among cigarette smokers than among nonsmokers and at least 60-fold more prevalent among two-pack-a-day smokers. No such characteristic has yet been produced despite diligent search.

These comments on the quantitative aspects of association apply also to the relationship of certain characteristics with lung cancer. Thus, a possible genetic basis to lung cancer has been suggested to some by the association between gastric cancer and blood group. The difference, in risk of developing gastric cancer, between blood groups A and O, however, is 20 percent, while the only study of lung cancer and blood groups⁸⁴ with which we are familiar shows a difference of 27 percent (and is not quite significant at the $P=0.01$ level.¹ Such differences are suggestive

for further work, but cannot be considered as casting much light on differences of magnitude, ninefold to 60-fold.

Measures of Differences

The comments in the last two paragraphs have utilized a relative measure of differences in lung-cancer risk. Since Berkson³² has argued that a relative measure is inappropriate in the investigation of smoking and mortality, we now discuss the use of relative and absolute measures of differences in risk. When an agent has an apparent effect on several diseases, the ranking of the diseases by the magnitude of the effect will depend on whether an absolute or a relative measure is used. Thus in Dorn's study⁸ of American veterans there were 187 lung-cancer deaths among cigarette smokers compared with an expectation of 20 deaths, based on the rates for nonsmokers. This yields a mortality ratio of 9.35 as a relative measure and an excess of 167 deaths as an absolute measure. For cardiovascular diseases there were 1,780 deaths among cigarette smokers compared to an expectation of 1,165. This gives a relative measure of 1.53 and an absolute measure of 615 deaths. Relatively, cigarettes have much larger effect on lung cancer than on cardiovascular disease, while the reverse is true if an absolute measure is used.

Both the absolute and the relative measures serve a purpose. The relative measure is helpful in 1) appraising the possible noncausal nature of an agent having an apparent effect; 2) appraising the importance of an agent with respect to other possible agents inducing the same effect; and 3) properly reflecting the effects of disease misclassification or further refinement of classification. The absolute measure would be important in appraising the public health significance of an effect known to be causal.

The first justification for use of the relative measure can be stated more precisely, as follows:

If an agent, A, with no causal effect upon the risk of a disease, nevertheless, because of a positive correlation with some other causal agent, B, shows an apparent risk, r , for those exposed to A, relative to those not so exposed, then the prevalence of B, among those exposed to A, relative to the prevalence among those not so exposed, must be greater than r .

Thus, if cigarette smokers have 9 times the risk of nonsmokers for developing lung cancer, and this is not because cigarette smoke in a causal agent, but only because cigarette smokers produce hormone X, then the proportion of hormone-X-producers among cigarette smokers must be at least 9 times greater than that of nonsmokers. If the relative prevalence of hormone-X-producers is considerably less than ninefold, then hormone X cannot account for the magnitude of the apparent effect (Appendix A).

¹Our attention has been called to a summary of three additional studies, which report no association between ABO blood groups and lung cancer, by Roberts JAF. Blood groups and susceptibility to disease. *Brit. J. Prev. & Social Med.* 11: 107-125, 1957.

The second reason for using a relative measure may be phrased as follows:

If two uncorrelated agents, A and B, each increase the risk of a disease, and if the risk of the disease in the absence of either agent is small (in a sense to be defined), then the apparent relative risk for A, r , is less than the risk for A in the absence of B.

The presence of other real causes thus reduces the apparent relative risk. If, for example, the relative risk of developing either disease I or disease II on exposure to A is the same in the absence of other causes, and if disease I, but not disease II, also has agent B present, then the apparent relative risk of developing disease I on exposure to A will be less than that for disease II (Appendix B).

The third reason for using a relative measure is:

If a causal agent A increases the risk for disease I and has no effect on the risk for disease II, then the relative risk of developing disease I, alone, is greater than the relative risk of developing disease I and II combined, while the absolute measure is unaffected.

Thus, in the Hammond-Horn study, the association of cigarette smoking and lung cancer was higher when only patients with a well-substantiated diagnosis of lung cancer were considered, and was lower when the group included questionable diagnoses. Using the relative risk reveals the stronger association of cigarette smoking and epidermoid-undifferentiated carcinoma than for adenocarcinoma. The absolute measure would not differentiate between the risk for these subgroups.

The Causal Hypothesis

We turn now to a consideration of some of the contradictions in the causal hypothesis, alleged by various authors. Fisher³⁵ has stated:

When the sexes are compared it is found that lung cancer has been increasing more rapidly in men relatively to women... But it is notorious, and conspicuous in the memory of the most of us, that over the last 50 years the increase of smoking among women has been great, and that among men (even if positive) certainly small. The theory that increasing smoking is 'the cause' of the change in apparent incidence of lung cancer is not even tenable in the face of this contrast.

The available statistics do not confirm Fisher's statement. According to the Tobacco Manufacturer's Standing Committee⁵³ male per capita consumption of cigarette tobacco in Great Britain increased from 1.9 pounds in 1906 to 8 pounds in 1956. Female per capita consumption increased from essentially zero, in

1906, to 3.1 pounds in 1956. Far from making the causal hypothesis untenable, these results are entirely consistent with it, and constitute, in fact, one of the links in the chain of evidence implicating cigarettes.

The fact that cigarette smoking was associated with a higher mortality not only from lung cancer but from many other causes of death was originally considered as a contradiction by Arkin³⁴. Commenting on the first Hammond-Horn report, he wrote:

It would thus appear that cigarette smoking is one of the causes of all ills and contributes to the overall death rate, remembering that this rate includes such causes as accident, homicide, etc. It seems quite clear that cigarette smoking is a symptom, not a cause. It is possible – even though this is a conjecture – that they type of person who is careful of his health is less likely to be a cigarette smoker and that the cigarette smoker is likely to be the person who generally takes greater health risks.

Both the later Hammond-Horn⁹ report and the study of American veterans⁸ show no difference between cigarette and noncigarette smokers in mortality from accidents, violence, and suicide. If nonsmokers are biologically self-protective, it is only with respect to non-accidental causes of death.

Berkson³² also has pointed to the multiple findings in both the Hammond-Horn and the Doll-Hill results and concluded that the observed associations may have some other explanation than a causal one. He suggests three: 1) "The observed associations are 'spurious' 2) The observed associations have a constitutional basis. Persons who are nonsmokers, or relatively light smokers, are the kind of people who are biologically self-protective, and biologically this is correlated with robustness in meeting mortal stress from disease generally. 3) Smoking increases the 'rate of living' (Pearl), and smokers at a given age are, biologically, at an age older than their chronologic age."

One might ask why the finding of an association with a number of diseases, rather than just one, is necessarily contradictory and must be regarded as supporting the constitutional hypothesis. Arkin³⁴ supplied no answer, while the relevant statements of Berkson³² on this point were:

For myself, I find it quite incredible that smoking should cause all these diseases.

When an investigation set up to test the theory, suggested by evidence previously obtained, that smoking causes lung cancer, turns out to indicate that smoking causes or provokes a whole gamut of diseases, inevitably it raises the suspicion that something is amiss.

It is not logical to take such a set of results [e.g., an association of smoking with a 'wide variety of

diseases'] as confirming the theory that tobacco smoke contains carcinogenic substances which, by contact with the pulmonary tissues, initiate cancerous changes at the site of contact.

We see nothing inherently contradictory nor inconsistent in the suggestion that one agent can be responsible for more than one disease, nor are we lacking in precedents. The Great Fog of London in 1952 increased the death rate for a number of causes, particularly respiratory and coronary disease, but no one has given this as a reason for doubting the causal role of the Fog. Tobacco smoke, too, is a complex substance and consists of many different combustion products. It would be more "incredible" to find that these hundreds of chemical products all had the same effect than to find the contrary. A universe in which cause and effect always have a one-to-one correspondence with each other would be easier to understand, but it obviously is not the kind we inhabit.

The apparent multiple effects of tobacco do raise a question with respect to the mode of action, however, and since this question is related to another alleged contradiction – the apparent lack of an inhalation effect – we shall discuss them together. What mode of action, it has been asked, can one postulate to explain these diverse effects? Two remarks are in order: 1) The evidence that tobacco is a causal agent in the development of other diseases seems weaker than the evidence for lung cancer simply because the effects are smaller. While we could not exclude the possibility that cigarettes play a causal role in, for instance, the development of arteriosclerotic-coronary heart disease, the possibility that a common third factor will be discovered, which explains a 70 percent elevation in risk from coronary heart disease among cigarette smokers, is less remote than the possibility that the ninefold risk for lung cancer will be so explained. 2) Accepting, for the sake of discussion, the causal role of cigarettes for any disease showing an elevated mortality ratio, no matter how small, the presence of other causes will be manifested in a lowered mortality ratio. Thus, even if cigarette consumption causes an elevation of 70 percent in mortality from coronary heart disease, other causes of great importance must also be present, as is manifested by the high mortality from this disease among nonsmokers. The existence of a small number of nonsmokers who develop lung cancer is a definite indication, by the same token, that cigarettes are not an absolutely necessary condition and that there are other causes of lung cancer.

If tobacco smoke does have multiple effects, each of these effects must be studied separately because of the complex nature of the agent. To postulate in advance that a single mode of action will be found to characterize them all is an unwarranted oversimplification. It is generally accepted, for example, that tobacco smoke causes thromboangiitis obliterans

in susceptible humans by interfering with the peripheral circulation, and that it causes tumors when painted on the backs of susceptible mice because of the presence of carcinogenics in the tars. The *a priori* postulation of a single mode of action for these two effects is no substitute for detailed study of each.

As to the possible mode of action of tobacco smoke in inducing lung cancer, the evidence at this writing suggests direct action of substances in tobacco smoke on susceptible tissues with which they are in contact. Aside from background knowledge derived from experimental carcinogenesis which suggests this explanation, the following evidence favors it: 1) Cigarette smoke, which is usually drawn into the lungs is associated with mortality from lung cancer, while smoke from pipes and cigars, which is usually not inhaled, is not. 2) For sites with which smoke is in direct contact, whether or not inhaled, particularly buccal cavity and larynx, the type of tobacco used makes less difference in incidence. 3) In experimental carcinogenesis, which uses tobacco tars, tumors have appeared at the site of application, and their incidence has not yet seriously depended on the type of tobacco used. 4) The relative risk of lung cancer is higher among cigarette smokers who inhale than among those smoking the same number of cigarettes per day, but who do not inhale.

Several critics^{36,38,39} have stressed the failure of Doll and Hill⁶², in their preliminary report, to find a difference in risk between inhalers and noninhalers, but this finding was contradicted in three other studies^{4,68,69}. Further work on this point is desirable, but would be more convincing if a more objective measure were found of the amount of smoke to which human bronchial epithelium is exposed in the course of smoking a cigarette.

Why, it is sometimes asked, do most heavy cigarette smokers fail to develop lung cancer if cigarettes are in fact a causal agent? We have no answer to this question. But neither can we say why most of the Lübeck babies who were exposed to massive doses of virulent tubercle bacilli failed to develop tuberculosis. This is not a reason, however, for doubting the causal role of the bacilli in the development of the disease.

One cannot discuss the mode of action of tobacco without becoming aware of the necessity of vastly expanded research in the field. The idea that the subject of tobacco and mortality is a closed one requiring no further study is not one we share. As in other fields of science, new findings lead to new questions, and new experimental techniques will continue to cast further light on old ones. This does not imply that judgment must be suspended until all the evidence is in, or that there are hierarchies of evidence, only some types of which are acceptable. The doctrine that one must never assess what has already been learned until the last possible piece of evidence would be a novel one for science.

It would be desirable to have a set of findings on the subject of smoking and lung cancer so clear-cut and unequivocal that they were self-interpreting. The findings now available on tobacco, as in most other fields of science, particularly biologic science, do not meet this ideal. Nevertheless, if the findings had been made on a new agent, to which hundreds of millions of adults were not already addicted, and on one which did not support a large industry, skilled in the arts of mass persuasion, the evidence for the hazardous nature of the agent would be generally regarded as beyond dispute. In the light of all the evidence on tobacco, and after careful consideration of all the criticisms of this evidence that have been made, we find ourselves unable to agree with the proposition that cigarette smoking is a harmless habit with no important effects on health or longevity. The concern shown by medical and public health authorities with the increasing diffusion to ever younger groups of an agent that is a health hazard seems to us to be well founded.

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Appendix A

We feel obliged to give proof of the rather obvious statement on the magnitudes of relative risk because it has been suggested that the use of a relative measurement is merely "instinctive" and lacking in rational justification. Let the disease rate for those exposed to the causal agent, B, be r_1 and for those not exposed, r_2 , each rate being unaffected by exposure or nonexposure to the noncausal agent, A. Let $r_1 > r_2$. Of those exposed to A, let the proportion exposed to B be p_1 , and of those not exposed to A, let the proportion exposed to B be p_2 . Because of the assumed positive correlation between A and B, $p_1 > p_2$. Then

$$R_1 = \text{rate for those exposed to A} = p_1 r_1 + (1 - p_1) r_2$$

$$R_2 = \text{rate for those not exposed to A} = p_2 r_1 + (1 - p_2) r_2$$

$$(1) \frac{R_1}{R_2} = \frac{p_1 r_1 + (1 - p_1) r_2}{p_2 r_1 + (1 - p_2) r_2}$$

Since $p_1 > p_2$ and r_1/r_2 , it follows that $R_1/R_2 > 1$.

From (1) we obtain

$$\frac{p_1}{p_2} = \frac{R_1}{R_2} + \frac{1}{p_2} \frac{r_2}{r_1} \left[(1 - p_2) \frac{R_1}{R_2} - (1 - p_1) \right]$$

Since $p_1 > p_2$ and $R_1/R_2 > 1$, the second term on the right is positive and

$$\frac{p_1}{p_2} > \frac{R_1}{R_2}$$

Since p_1/p_2 is the ratio of the prevalence of B among those exposed to A relative to that among those not so exposed, and R_1/R_2 is the apparent relative risk, r , the statement is proved.

On the other hand, if the absolute difference, $R_1 - R_2$, is used, the relationship,

$$(R_1 - R_2) = (r_1 - r_2) (p_1 - p_2)$$

leads to no useful conclusion about $p_1 - p_2$.

Appendix B

The proof again is simple. Let r_{11} denote the risk of the disease in the presence of both A and B, r_{12} , the risk in the presence of A and absence of B, r_{12} , the risk in the absence of A and presence of B, and r_{22} the risk in the absence of both A and B. It is reasonable to assume $r_{22} = 0$, but the less restrictive specification $r_{22} < r_{12} r_{21} / r_{11}$ is sufficient for what follows. The proportion of the population exposed to B is denoted by p , and this, by hypothesis, is the same whether A is present or absent. Then

$$R_1 = \text{rate for those exposed to A} = p r_{11} + (1 - p) r_{12}$$

$$R_2 = \text{rate for those not exposed to A} = p r_{21} + (1 - p) r_{22}$$

and

$$\frac{R_1}{R_2} = \text{apparent relative risk} = \frac{r_{12} \frac{p}{1-p} \frac{r_{11}}{r_{12}} + 1}{r_{22} \frac{p}{1-p} \frac{r_{21}}{r_{22}} + 1}$$

Since $r_{22}/r_{21} < r_{12}/r_{11}$, the second factor is less than unity and

$$\frac{R_1}{R_2} < \frac{r_{12}}{r_{22}},$$

which proves the proposition.