

FILE NAME: Smoking (SMOK)

DATE: 1956 Feb

DOC#: SMOK007

DOCUMENT DESCRIPTION: Journal Article - Epidemiological
Tests of Theories on Lung Cancer Etiology



Volume 71, Number 2

FEBRUARY 1956

Published since 1873

CONTENTS

	<i>Page</i>
Epidemiology of leukemia —PHR review	103
<i>Gilcin F. Meadors.</i>	
Clues to suicide	109
<i>Edwin S. Shneidman and Norman L. Farberow.</i>	
Cardiovascular diseases and public health	115
<i>John W. Ferree.</i>	
The epidemic climate —PHR review	125
<i>Winston H. Price.</i>	
Unfinished business in maternal and child nutrition	139
<i>Marjorie M. Heseltine.</i>	
The use of insecticide treated cords for housefly control	144
<i>John W. Kilpatrick and H. F. Schoof.</i>	
Man's emergence toward health —The C.-E. A. Winslow lecture, 1955	151
<i>Henry van Zile Hyde.</i>	
Public health in Pennsylvania	160
<i>Berney F. Mattison.</i>	
Epidemiological tests of theories on lung cancer etiology	163
<i>William Haenszel.</i>	
Health services in civil defense —A symposium	173
Biological-medical considerations in atomic defense	173
<i>Edwin G. Williams and Samuel C. Ingraham II.</i>	
Radiological defense	181
<i>Simon Kinsman.</i>	
Chemical weapons	184
<i>Harry P. Kramer.</i>	

Continued ►



frontispiece

A laboratory technician determines blood-clotting time, information necessary to the safe use of anticoagulant drugs. (See story of the American Heart Association on page 115.)

Epidemiological Tests of Theories on Lung Cancer Etiology

By WILLIAM HAENSZEL

QUESTIONS on the etiologies of lung cancer cannot be resolved by a single, decisive experiment or set of observations, and a single study is not the natural unit for discussing the epidemiology of this disease. The major concern must be with the interrelationships of findings and their collation to see whether a chain of evidence stronger than any single component part can be forged. Information on a proposed etiology cannot be assessed without relating it to both positive and negative findings on alternate possibilities, drawn from animal experimentation and other laboratory work as well as from epidemiological studies. Also, with a subject under such active scrutiny as lung cancer, it is difficult to attempt to divorce facts already established from interpretations which may either be stated explicitly or merely be implied by investigators through their choice of specific studies to be pursued. Under these conditions, a better perspective on epidemiological issues in lung cancer studies may be gained by viewing them in the perspective of possible future work. Since interrelationships of individual findings are the main concern, this paper

deals more with the ideas underlying a set of studies than with the tactical details of any single study.

Increase in Lung Cancer

If no real increase in lung cancer existed, all associations between lung cancer and exposure to atmospheric pollution, cigarette smoking, or other exogenous agents recently introduced into the environment would be suspect as not pointing to possible etiological relationships. A few persons still maintain that the recorded increase in lung cancer incidence and mortality is fictitious and has resulted from improved diagnosis (1), but this is no longer a popular position (2). Among the reasons for accepting a real increase in lung cancer mortality are the sex differences in rate of increase and the magnitude of the current, continuing increase (3).

One purpose for inquiries on the increase in risk would be to provide more precise quantitative estimates than are now available from mortality data which may later prove useful for reconciliation with numerical measures of exposure to suspected agents. For this reason, anyone proposing to study the effect of possible misdiagnosis of lung cancer as tuberculosis (4) or some other cause should relate these effects to data produced by the death registration system. Samples of deaths from lung cancer and other causes taken from vital statistics sources could be compared with autopsy protocols and other diagnostic evidence. Evaluation of the

Mr. Haenszel is head of the Biometry Section, Biometry and Epidemiology Branch, National Cancer Institute, Public Health Service. He presented this paper at a joint session of the Biometrics Society and the Institute of Mathematical Statistics, Chapel Hill, N. C., April 23, 1955

two sources of error in official statistics, (a) deaths from other causes erroneously recorded as lung cancer and (b) lung cancer deaths attributed to other causes, would be rendered difficult by the selective character of autopsy statistics. However, the effort should be made. A useful minimum objective would be to determine how many lung cancer cases remain undiagnosed at present. Farber reported that in a series of 1,070 morphologically proved cases of bronchogenic carcinoma, 61 percent were not positively diagnosed prior to autopsy (5). Undoubtedly, many of these deaths were not recorded as lung cancer on the death certificate.

Environmental Agents

The working hypothesis for most investigators has been that the probable causes of lung cancer are to be found among environmental agents (2). The association of the high prevalence of cancers for several other sites, particularly the mouth, with specific customs found only in certain parts of the world strengthens the belief that direct contact with known or suspected carcinogens may be involved (6). On the assumption that agents with opportunity for direct contact with lung tissue are the most likely candidates, efforts to establish etiological relationships between lung cancer and environmental agents have been directed into three main areas: (a) airborne agents encountered in special occupations; (b) atmospheric pollutants, particularly those resulting from combustion of hydrocarbons; and (c) smoking of tobacco.

To assert that an agent is etiologically related to lung cancer simply implies that its removal from a defined population will result ultimately in a marked reduction of lung cancer. The population must be defined in a manner which safeguards against an effect being produced merely by the process of selection and classification. The concept does not require detailed specification of a mechanism producing the effect. Goldberger's finding that pellagra may be prevented by diet was no less valid because subsequent work led to the identification of the vitamin B complex and, finally, to nicotinic acid as the effective agent. This statement does not imply that ideas on mechanisms

are not helpful; to the contrary, they may suggest situations in which data can be collected and tested.

Occupational Carcinogens

There is general agreement on the etiological significance of several occupational exposures, and such findings have been important in establishing the principle of multiple etiologies for lung cancer. Long-term observations of closed populations have convinced most people that the Schneeberg and Joachimsthal miners (7, 8) and certain groups of chromate workers (9, 10) were subjected, by virtue of their occupations, to excessive lung cancer risks. The evidence on chromate workers is purely epidemiological, not confirmed by animal experimentation, and was first suspected on the basis of clinical observations. Although many investigators have deduced from the Schneeberg and Joachimsthal observations that radiations emitted from radon were responsible, Lorenz felt that the case had not been firmly established and that other possibilities, such as dust pneumoconiosis, had not been conclusively ruled out (11).

Excess lung cancer risks detected by examination of occupational mortality data, such as data on workers employed in the preparation of coal tar products and producer gas (12), have also been generally accepted as reflecting an etiological relationship between lung cancer and some suspected carcinogenic agent in these products. Nor is there any great disposition to question the status of agents detected by clinical observations and retrospective studies of agents such as arsenic dust, nickel carbonyl, asbestos dust, and coke oven fumes (13). When the study results are reviewed to pick up occupational exposures which appear repeatedly, the danger of being misled by a highly unusual result in a single study is minimized. Additional occupational risks will no doubt be demonstrated in the future. However, because of the small numbers of workers exposed, the further denumeration of very restricted types of risks will not be crucial in working out the epidemiological details of lung cancer. This statement would not apply to the common and widespread agents contributing to atmospheric pollution, including hydrocarbon combustion products

such as industrial and heating plant wastes and motor vehicle exhausts.

Atmospheric Pollutants

To date, atmospheric pollution theories have not been well documented by demonstrations of excess risk among workers with heavy exposures to common atmospheric pollutants such as may exist in railroad yards, oil refineries, and congested urban areas. With the advent of group insurance and pension plans, the methodological problems of such inquiries have become much simpler. Several cohorts can be located for study. The National Cancer Institute is following a group of 1,100,000 railroad employees who have been in the industry 10 years or longer, including station, office, yard, and shop employees, as well as train crews. Rather detailed occupational histories are available and, with the accumulation of mortality data over several years, such specific points as the effects of dieselization, prolonged exposure to smoke in railroad tunnels, and metal dust exposures in shops may be looked into. The important feature is that work histories and exposures be specified in some detail. Significant effects may be diluted and overlooked by considering only gross company or industry experience.

The widespread use of petroleum products makes it very desirable to gather data on workers in that industry. Some medical departments of the major oil companies have staffs well equipped to undertake such studies. The major problem here, as elsewhere, is to secure access to company records and to rearrange data organized to meet other administrative needs. In areas where petroleum operations are concentrated, data might be collected on a geographic rather than an industrywide basis. At least one study is under way in Oklahoma which may yield some information on lung cancer risks among oil industry employees.

Those advancing atmospheric carcinogen theories have pointed to the sizable urban-rural differentials in lung cancer risk (14), although some further assumptions are required to reconcile this hypothesis with the great excess risk observed among males. The presence of carcinogenic substances in urban atmospheres has been repeatedly demonstrated by experi-

ments with mice (15, 16). Further epidemiological work has been hampered by the inability to classify individuals in the general population quantitatively with respect to atmospheric exposures. Meaningful histories are hard to collect, and in mobile populations, problems of classification by residence histories become complex. When leads on specific types of atmospheric pollutants are obtained from studies of special situations, the way may then be opened for return to the problem of reclassifying the general population with respect to special exposures with greater chance for success.

Smoking of Tobacco

Although at least 14 retrospective clinical studies (17) have reported on the association of smoking and lung cancer, these studies have been criticized on a variety of technical grounds. The objections advanced cover such points as interviewer bias (interviewers in some studies knew the identity of lung cancer patients and controls at the time of interview), and bias arising from selection factors associated with hospital admission (in most studies only hospitalized lung cancer patients were interviewed). However, the objection based on knowledge of the identity of patients and controls ignores the evidence of Doll and Hill (18) that males erroneously interviewed as lung cancer cases, as established by later events, showed smoking histories characteristic of the control rather than of the lung cancer series. Because of possible selection factors involved in taking up the smoking habit, some feel that the tobacco-lung cancer associations reflect associations with other common, but still unidentified factors.

The present data on associations between smoking and lung cancer are the most extensive and afford the most opportunities for discussing additional studies. For orientation, the type of evidence now on hand may be compared with the epidemiological findings for cholera, pellagra, and dental caries, all diseases in which animal experimentation played a minor role, at least in the early phases of the investigation (19-25).

On review, the basic core of associations on smoking and lung cancer must appear as impressive as any produced in these other investi-

gations. However, lung cancer does not present the features of geographic localization characteristic for cholera, pellagra, and the absence of dental caries, which made it possible to elaborate in a rather straightforward manner the basic associations with water supplies suspected of contamination (cholera), diet (pellagra), and fluoridated water (dental caries) with corroborative detail and combinations of isolated special situations. Such detail is helpful in ruling out some association as not significant etiologically; in this manner, for example, the associations between cholera and altitude (within London) and between pellagra and mill village occupations could be discarded as not significant. For lung cancer, there are as yet no counterparts, for example, to the cholera patient in an isolated rural area who regularly sent for water from the famous Broad Street pump (19); to the absence of pellagra among doctors, nurses, and attendants in mental institutions, although the disease was common among patients; to the peculiar age distribution for pellagra in a children's institution where the disease was limited to children between the ages of 6 and 12; to differential attack rates for dental caries by gradations of exposure to fluoridated supplies among natives and immigrants; and to the sequence of dental events following shifts in the source of a community water supply. Collection of such details generally results from the study of populations. This is one of the reasons why forward studies on lung cancer among defined population cohorts are so important.

Furthermore, the epidemiological models for cholera, pellagra, and dental caries have been put to the test in the successful application of control measures. For pellagra, only the addition of meat and milk to the diet was involved (26). Fluoridation effects could be observed under controlled conditions because of the happy accident of public water supplies; if private wells were the only source of water, the problem would have been complicated by self-selection of families fluoridating their own supplies. The test of Snow's conclusions on cholera (19), which required implementation through administrative decisions on methods for control of public water supplies, occurred

much later, more than 10 years after he had formulated them.

The right combinations of circumstances to permit such straightforward tests of most of the proposed lung cancer etiologies are not present now. Thus, the immediate lines for further work on the nature and meaning of the smoking-lung cancer associations are to develop reasonable facsimiles to tests by control measures and to assemble supporting, corroborative details from population studies, not overlooking any negative evidence which may appear.

Substitutes for Direct Tests

As a substitute for a direct test by control measures of the smoking-lung cancer model one may look for groups in which smoking is either proscribed for religious reasons or does not otherwise form part of the cultural pattern.

Two of the four basic study elements required are at hand: data on the distribution of smoking habits in the United States population (collected as part of the Current Population Survey for February 1955), and data on lung cancer mortality (from publications of vital statistics offices). The major problems would be to secure the cooperation of the groups selected and to develop procedures to obtain the counterparts of these data for their memberships. To avoid artifacts which might be introduced by classification procedures, the primary test must be whether the overall lung cancer mortality in the group studied was markedly less than for an appropriate segment of the population of the United States and commensurate with differences in the smoking patterns. To this, other refinements may be added, such as observing whether mortality differences between the study and control populations disappear when specific comparisons are made by amount of tobacco smoked.

The limited number of countries which can provide reliable diagnostic data on causes of illness and death has discouraged similar studies of groups abroad which have unusual smoking patterns. However, special study situations may be encountered. One illustration is cited, without judgment as to its intrinsic merit. The director of the Hadassah medical organization recently reported the absence of a single case

of lung cancer among Yemenite Jews in Israel during the past 15 years, and he further observed that they did not smoke cigarettes but used a form of Oriental water pipe (27). Israel is a country with western standards of medical care and this lead may be worth pursuing. In these matters, the importance of reviewing the primary sources of population, morbidity, and mortality data should be stressed.

Other clues may lead indirectly to population groups with unusual smoking histories. For example, Steiner (6), on the basis of necropsy evidence in Los Angeles, has found a possible exception among Mexicans to the usual sex ratio for lung cancer; the proportion of Mexican women with lung cancer at autopsy approaches the proportion for Mexican men. This suggests the need for further studies among Mexicans to confirm the facts and to uncover possible reasons for the aberrant sex ratio for lung cancer. This might conceivably lead to the finding of a group of unusually heavy smokers among women, a useful contrast to the experience of abstainers.

Corroborative Details

Additional details on the nature of the smoking-lung cancer relationship should be assembled from large-scale forward studies. These possibilities were obviously in the minds of those who planned the American Cancer Society and the National Cancer Institute-Veterans Administration studies. Both study groups consist mainly of men between the ages of 50 and 69, the ages of highest lung cancer incidence.

One approach is to expand the evidence on the nature of the association by detailed cross-classification. Epidemiologists have long accepted the principle that the etiological significance of an association is enhanced if it can be shown to persist within a variety of sub-universes. The National Cancer Institute-Veterans Administration cohort can be subdivided with respect to occupation and industry. By lengthening the observation period to several years, further tests can be applied in both studies, including checks on the consistency of regression relationships between lung cancer mortality and amounts of tobacco smoked for

several occupational groups and for urban and rural residents.

Additional tests can be pursued by relating age at death to "age started smoking" to see if any consistent pattern emerges.

Studies Among Women

Unfortunately for study purposes, the spread of "age started smoking" is not too great among men, and it may be hard to assemble sizable cohorts for the more unusual combinations of year of birth and "age started smoking." Women would be more promising subjects, since women of all ages began smoking in large numbers during the 1930 decade, and duration of smoking by women is not so closely tied to chronological age. For this reason, more prospective and retrospective studies on smoking and lung cancer among women would be rewarding. In addition to the one series of studies on smoking among women reported by Doll and Hill (28), two retrospective studies are known to be under way. The relative rarity of lung cancer among women imposes severe study handicaps and has undoubtedly deterred other efforts.

Potential cohorts for followup would include employed women covered by group life insurance policies. To minimize turnover and loss to observation it would be desirable to restrict the cohort to employees with several years' service.

Studies of lung cancer among women should establish what part, if any, of the sex differential in lung cancer mortality (or incidence) disappears when comparisons are made specific for smoking class. The fragmentary Doll-Hill data suggest that a good part, but not all, of the sex differential may be accounted for in this manner.

Indirect Checks

Retrospective and prospective studies may be viewed as efforts to secure etiologically meaningful data, which official vital statistics sources cannot provide, since they are limited to classification by standard demographic variables. There is another transitional bridge by which vital statistics data on lung cancer deaths can

be utilized. By taking information on smoking patterns in the general population (collected in Current Population Survey for February 1955) and applying to them the data on absolute and relative lung cancer risks by smoking class as reported in the preliminary results of the American Cancer Society study (29) and in several retrospective studies (30), the "expected" distribution of lung cancer deaths can be computed by sex, urban or rural residence, geographic region, and broad occupational groups, on the assumption that risks by smoking class in the groups studied hold also in the total population. Comparison of the observed and "expected" numbers of deaths would then show how much of the prevailing variation in lung cancer mortality can be accounted for by considering smoking histories. In this manner, some useful consistency checks on the smoking-lung cancer model would be provided.

Such consistency checks need not be confined to smoking histories. The Current Population Survey material illustrates an economically feasible means for remedying some deficiencies in standard population classifications. Although many investigators have expressed the need for procuring information on the population distribution of characteristics under study, they have often been deterred by the cost. Probability sampling methods for gathering such data can provide a powerful tool to the epidemiologist.

Other Possible Factors

Turning from suspected environmental agents with properties which permit direct contact with lung tissue, several possible causes of lung cancer remain. There is the class of environmental agents which do not come in direct contact with lung tissue. Closely related would be possible tissue changes induced by virus and other infectious agents. Constitutional susceptibility might also be considered. If some persons have a predisposition to attacks on lung tissue by some morbid process, the rise in lung cancer might be due to the suppression of "competitive" respiratory causes, such as tuberculosis and pneumonia. Finally, there is the possibility of the association of smoking with other physical, psychological, and emo-

tional factors which may be engendered by the processes influencing persons to take up smoking.

In dealing with lung cancer, where prospects for tests of etiological relationships by trial of control measures are remote, other hypotheses, however unlikely, and the collection of evidence to support or discredit them should be encouraged. The pursuit of other lines of investigation will be useful. If results are positive, another effect of lung cancer will have been discovered; if negative, they will buttress the interpretations applied to effects already known.

Gilliam, in a general discussion of chronic disease epidemiology, alluded briefly to a variety of items investigated by him in a study of lung cancer patients and controls, using the retrospective, case-history method (31). These items ranged from color of eyes and use of dentures to histories of illnesses and use of general anesthetics. As he hastens to say, such individual findings cannot be used for any generalizations. However, it may be worth while to inquire systematically into other findings collected but never deemed worthy of report. Several of the other early retrospective studies were "shotgun" inquiries and collected information on a variety of suspected agents and exposures. Collectively, these results might prove useful for testing and discriminating between hypotheses and the planning of further studies.

Several studies exploring characteristics differentiating smokers and nonsmokers may be expected. The question of differences between the two groups arises because smokers select themselves; smoking is not a treatment which can be studied experimentally by randomized application to a population. There is a wide range of possibilities for retrospective studies on the physical, psychological, and emotional attributes of smokers and nonsmokers. The demonstration of an item as being associated with smoking history is essentially a screening device. The further test is whether the item, when applied to a population, produces differences in lung cancer risks equal in magnitude to those yielded by smoking history classifications (if smoking history is uncontrolled), or whether an effect is observed when smoking history is controlled by classification.

Association With Other Illnesses

Some theories on the subsequent increased risk of lung cancer among persons with histories of respiratory illnesses such as influenza, pneumonia, bronchitis, and tuberculosis, based usually on clinical and pathological impressions, have been reviewed by Doll (32), who continues on to point out some observations inconsistent with these theories. No associations of lung cancer with the presence or absence of an antecedent illness have yet been established by observations on populations through the use of retrospective or prospective studies. Retrospective studies are handicapped in this field, because patients with lung cancer and other respiratory disorders apparently recall previous respiratory ailments more readily than do other persons. There are some possibilities for forward studies on cohorts known to have recovered from specific illnesses, free from the "recall" bias in the retrospective approach, which may be exploited. For example, records can be assembled of World War I veterans who had influenza and/or pneumonia in 1918. These veterans can be traced forward in time to determine their lung cancer mortality experience. (A study of British veterans (40) has been published recently.) From civilian life, one could draw on recovered pneumonia cases reported to health departments in the 1930 decade, when these agencies had active programs based on pneumococcus typing and distribution of serum.

If excess lung cancer mortality among such groups were demonstrated, this would not necessarily be a result of effects of antecedent illnesses. If constitutional predisposition of lung tissue were a factor, the rise in lung cancer mortality might be due to the suppression of tuberculosis and pneumonia as causes of death. If a genetic basis for constitutional predisposition to lung cancer were postulated, other tests could be devised. One approach would be to assemble lists of relatives of diagnosed cases of lung cancer for followup to determine lung cancer mortality. Lists of familial contacts could be assembled from records maintained in tuberculosis control programs. Investigations of this character might be undertaken more readily in some European countries, where pop-

ulation mobility is low and more comprehensive population record systems exist.

Retrospective and Forward Studies

The preceding sections have emphasized the wide range of possibilities for the use of retrospective and forward study techniques. Retrospective, case-history studies use as their point of departure diagnosed cases of a disease and matched controls and compare antecedent events in their previous histories. Prospective, or forward, studies start with the assembly at a fixed point in time of defined cohorts classified with respect to certain attributes, trace them forward in time, and note events occurring subsequently.

Perhaps the major criticism of retrospective studies for lung cancer has been that diagnosed cases have generally been drawn from hospital populations. Positive association between two diseases, not present in the general population, may be produced when hospital admissions alone are studied, because persons with a combination of complaints are more likely to require hospital treatment (33, 34). Smoking is not an illness, and for lung cancer it is difficult to see how the smoking history could have any influence on hospital admission. Lung cancer is a serious disease normally requiring hospitalization, and roughly four-fifths of all diagnosed cases are hospitalized (35). The proportion is even higher when microscopically confirmed cases alone are considered. There would have to be extraordinary differences in smoking histories between hospitalized and nonhospitalized patients and controls to upset inferences drawn from hospitalized cases (36). So far, the results of forward population studies on excess lung cancer risks among smokers as compared to nonsmokers have agreed in general with those of the retrospective studies. This suggests that biases entering into the selection of hospitalized cases and controls studied retrospectively are probably not the source of the associations noted.

The fundamental assumption underlying retrospective studies and the estimation therefrom of differences in risks between population groups is that the diagnosed cases and controls each be representative of the universe chosen

for investigation. Although there are precautions which can be taken in devising a sampling plan, this representative property cannot be guaranteed merely from internal examination of a single set of data. One must be guided on this point by the comparison of results from several studies and judgment as to the possible biases operating in any setting.

Forward population studies have been questioned on the grounds that the cohorts have not been selected by probability sampling methods and that individual study results cannot be generalized to the total population. The expense involved in tracing cohorts drawn from the general population by probability sampling methods would be great and most investigators have been forced to look for populations followed routinely for other purposes, such as persons covered by employment or insurance benefits.

The criticisms of unrepresentative sampling would appear to disregard the experience available from actuarial sources. There are two common types of insurance: "ordinary" policies, which require applicants to pass a physical examination, and "industrial" policies, which undergo some underwriting selection but require no physical examination. Policyholders would scarcely meet the usual criteria for representative samples. The Metropolitan Life Insurance Co. has published extensive data on the mortality experience of their industrial policyholders and finds rather close agreement with the mortality experience of the general population, after appropriate adjustments for age, sex, and race composition (37). Data drawn from actuarial experience and reported in such sources as *Length of Life* (38) and *The Statistical Bulletin*, a monthly publication of the Metropolitan Life Insurance Co., indicate that the relative patterns of mortality with respect to cause, age, sex, race, and geographical region in insured populations have their counterparts in general mortality experience despite some differences in magnitude of rates. The cohorts assembled for smoking and lung cancer investigations do not appear to have been subjected to more rigorous selection than that encountered by industrial policyholders, nor is there reason to believe that the selection effects which did exist discriminated between smokers and nonsmokers. Even when stronger selection

effects on mortality experience exist, as in the case of ordinary policyholders, it is well known that the selection effects of physical examinations on mortality experience wear off quickly; very conservatively, in 10 years or less (39), usually in about 5 years. If there is any question about the prospective study results on the association of smoking and lung cancer being affected by selection, the conservative course would be to discount the first few years' experience and to require that the early results be confirmed by later experience after selection effects have worn off.

The collation of experience from several studies is also a safeguard against error in generalizing from forward studies on lung cancer. Data from prospective studies may be subclassified by other population characteristics and further checked for internal consistency. With these precautions, the dangers of drawing inferences from forward and retrospective studies inapplicable to the general population seem rather remote.

Summary

The size of the lung cancer problem, as indicated by the number of lives at stake and the economic implications of any potential control measures which might later be advanced, should not blind investigators to the many possibilities for studies similar to those on other chronic diseases which have yielded some of their secrets to the epidemiological approach. Diseases showing pronounced variations in risk among population subgroups are the more amenable to epidemiological study; and lung cancer falls into this category. Studies on human populations should continue to play an important role in delineating possible etiological relationships for lung cancer, the mechanisms for which could then be elaborated by animal experimentation.

Progress must come by the cross-checking of the several results of epidemiological studies, animal experimentation, and other laboratory findings. The issues will probably be settled by an evolutionary process, as was the fluoride-dental caries relationship. Gradually, the meaning of certain associations will become accepted. Dissent will die off and the debate will shift to the many other points in any

epidemiological models still requiring elaboration.

REFERENCES

- (1) Rigdon, R. H., and Kirchoff, H.: Smoking and cancer of the lung—Let's review the facts. *Texas Rep. Biol. & Med.* 11: 715-727 (1953).
- (2) Clemmesen, J., Nielsen, A., and Jensen, E.: Mortality and incidence of cancer of the lung in Denmark and some other countries. In *Cancer of the Lung; A symposium*, edited by Dr. J. Clemmesen, reprinted from *Acta Unio Contra Cancerum*. Paris, Council for International Organizations of Medical Sciences, 1953, 210 pp.
- (3) Dunn, H. L.: Lung cancer in the twentieth century. *J. Internat. Coll. Surg.* 23: 326-342 (1955).
- (4) Gilliam, A. G.: Some aspects of the lung cancer problem. *Mal. Med.* 116: 163-174 (1955).
- (5) Farber, S. M.: Lung cancer. Springfield, Ill., C. C. Thomas, 1954, p. 4.
- (6) Steiner, P. E.: Cancer: Race and geography. Baltimore, Williams & Wilkins Co., 1954, 363 pp.
- (7) Rosotoski, O., Saupe, E., and Schmorl, G.: Die bergkrankheit der erzbergleute in Schneeberg in Sachsen. *Zeitschr. F. Krebsforschung* 23: 360-384 (1926).
- (8) Peller, S.: Lung cancer among mine workers in Joachimsthal. *Human Biology* 11: 130-143 (1939).
- (9) Brinton, H. P., Frasier, E. S., and Koven, A. L.: Morbidity and mortality experience among chromate workers. *Pub. Health Rep.* 67: 835-847 (1952).
- (10) Machle, W., and Gregorius, F.: Cancer of the respiratory system in the United States chromate-producing industry. *Pub. Health Rep.* 63: 1114-1127 (1948).
- (11) Lorenz, E.: Radioactivity and lung cancer; A critical review of lung cancer in the miners of Schneeberg and Joachimsthal. *J. Nat. Cancer Inst.* 5: 1-15 (1944).
- (12) Kennaway, E. L., and Kennaway, N. M.: A further study of the incidence of cancer of the lung and larynx. *Brit. J. Cancer* 1: 260-298 (1947).
- (13) Hueper, W. C.: Recent developments in environmental cancer. Reprinted, with additions, from the *A. M. A. Archives of Pathology* 58: 360-399, 475-523, 645-682 (1954).
- (14) Hueper, W. C.: Environmental lung cancer. *Indust. Med. and Surg.* 20: 49-62 (1951).
- (15) Leiter, J., Shimkin, M. B., and Shear, M. J.: Production of subcutaneous sarcomas in mice with tars extracted from atmospheric dust. *J. Nat. Cancer Inst.* 3: 155-165.
- (16) Kotin, P., Falk, H. L., Mader, P., and Thomas, M.: Aromatic hydrocarbons. *Arch. Ind. Hyg. and Occup. Med.* 9: 153-163 (1954).
- (17) Dorn, H. F.: The relationship of cancer of the lung and the use of tobacco. *The American Statistician* 8: 7-13 (1954).
- (18) Doll, R., and Hill, A. B.: Smoking and carcinoma of the lung. *Brit. M. J.* 2: 745 (1950).
- (19) Snow, J.: *Snow on cholera*. New York, The Commonwealth Fund, 1936, 191 pp.
- (20) Goldberger, J., Wheeler, G. A., and Sydenstricker, E.: A study of the relation of diet to pellagra incidence in seven textile-mill communities of South Carolina in 1916. *Pub. Health Rep.* 35: 648-713 (1920).
- (21) Goldberger, J., Wheeler, G. A., and Sydenstricker, E.: Pellagra incidence in relation to sex, age, season, occupation, and "disabling sickness" in seven cotton-mill villages of South Carolina during 1916. *Pub. Health Rep.* 35: 1650-1663 (1920).
- (22) Goldberger, J., Wheeler, G. A., and Sydenstricker, E.: A study of the relation of factors of a sanitary character to pellagra incidence in seven cotton-mill villages of South Carolina in 1916. *Pub. Health Rep.* 35: 1701-1714 (1920).
- (23) Goldberger, J., Wheeler, G. A., and Sydenstricker, E.: A study of the relation of family income and other economic factors to pellagra incidence in seven cotton-mill villages of South Carolina in 1916. *Pub. Health Rep.* 35: 2673-2714 (1920).
- (24) Bibby, B. G., and Brudevold, F.: The external action of fluorides and other agents on the teeth in the prevention of tooth decay. In *Fluoridation as a public health measure*, edited by J. H. Shaw. Washington, D. C., American Association for the Advancement of Science, 1954, pp. 148-178.
- (25) U. S. Public Health Service: Epidemiological studies of fluoride waters and dental caries. Collection of reprints from Public Health Reports, 1938-44.
- (26) Goldberger, J., Waring, C. H., and Tenner, W. F.: Pellagra prevention by diet among institutional inmates. *Pub. Health Rep.* 38: 2361-2368 (1923).
- (27) *New York Times*. Feb. 1, 1955.
- (28) Doll, R., and Hill, A. B.: A study of the aetiology of carcinoma of the lung. *Brit. M. J.* 2: 1271-1286 (1952).
- (29) Hammond, E. C., and Horn, D.: The relationship between human smoking habits and death rates. *J. A. M. A.* 155: 1316-1328 (1954).
- (30) Cutler, S. J., and Loveland, D. B.: The risk of developing lung cancer and its relationship to smoking. *J. Nat. Cancer Inst.* 15: 201-211 (1954).
- (31) Gilliam, A. G.: Opportunities for application of epidemiologic method to study of cancer. *Am. J. Pub. Health* 43: 1247-1257 (1953).
- (32) Doll, R.: Bronchial carcinoma: Incidence and aetiology. *Brit. M. J.* 2: 521-527 (1953).

- (33) Beckson, J.: Limitations of the application of fourfold table analysis to hospital data. *Biometrics Bull.* 2: 47-53 (1946).
- (34) White, C.: Sampling in medical research. *Brit. M. J.* No. 4849: 1284-1288, Dec. 12, 1953.
- (35) U. S. Public Health Service, National Cancer Institute: Cancer illness in ten urban areas of United States. *Cancer Morbidity Series Nos.* 1-10, 1950-52.
- (36) Kraus, A. S.: The use of hospital data in studying the association between a characteristic and a disease. *Pub. Health Rep.* 69: 1211-1214 (1954).
- (37) Dublin, L., and Spiegelman, M.: Health progress among industrial policyholders 1946 to 1950. *Soc. Actuaries Tr.* 3: 294-328 (1951).
- (38) Dublin, L. L., Lotka, A. J., and Spiegelman, M.: *Length of life*. Rev. ed. New York, Ronald Press Co., 1949, p. 193.
- (39) Jordan, C. W.: *Life contingencies*. New York, Society of Actuaries, 1952, p. 30.
- (40) Case, R. A. M., and Lea, A. J.: Mustard gas poisoning, chronic bronchitis, and lung cancer. An investigation into the possibility that poisoning by mustard gas in the 1914-18 war might be a factor in the production of neoplasia. *Brit. J. Prev. & Social Med.* 9: 62-72 (1955).

Ninth Annual Seminar on Seafood Sanitation

The ninth annual Seminar on Seafood Sanitation, sponsored by the Virginia and Maryland State Health Departments, was held in Solomons, Md., September 27-29, 1955. More than 50 persons attended the 5 sessions, which included an inspection of an oyster-packing house and a visit by boat to a soft-clam harvesting area on the Patuxent River.

The first Seminar on Seafood Sanitation was held in 1946 because seafood sanitation specialists found that their work required broad up-to-date technical knowledge. In addition to the common food plant sanitation problems, they were concerned with the construction and operation of municipal and private sewage disposal works; they had to make bacteriological, hydrographic, and sanitary surveys of shellfish-growing areas; and they were obliged to apply the results of these studies to decisions on the suitability of an area for shellfish culture. The seminar has provided a forum where bacteriologists, sanitarians, and sanitary engineers working with seafood sanitation in the Chesapeake Bay area can exchange information on such problems of mutual interest.

Many seafood sanitation problems encountered by county, State, and Federal personnel were discussed at the 3-day meeting. These included sanitary surveys of shellfish-growing areas, general food plant sanitation, sanitation of oyster-shucking plants, sanitation problems in the crabmeat industry, sanitary

problems in the new Chesapeake Bay soft-clam industry, preservation of food by radioactive sterilization, and a discussion of the relative merits of State certification of processors of breaded seafood.

Included in the agencies represented in the discussions were State health departments of Maryland, Virginia, South Carolina, Georgia, and the District of Columbia; New York State Department of Conservation; Maryland county health departments which have seafood sanitation programs; the Food and Drug Administration and the Public Health Service; and the Fish and Wildlife Service. The seafood industry was represented by officials of the National Fisheries Institute, the Oyster Institute of North America, and the Oyster Growers and Dealers Association of North America, Inc.

William Ballard, president of the Oyster Growers and Dealers Association of North America, Inc., and operator of one of the world's largest oyster-shucking and packing plants, told of his industry's dependence on sanitation and expressed the opinion that the future of the seafood industry rested with the accomplishments of the fisheries research scientists and with the seafood sanitation specialists.

The participants recommended that the health departments of Maryland and Virginia sponsor another seafood sanitation seminar in 1956.

