Epidemiological Methods and Inferences in Studies of Noninfectious Diseases

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DURING THE PAST FEW YEARS, the epidemiological approach has been applied increasingly to the study of noninfectious diseases, such as cancer and heart disease. Various methods of study have been used, and various inferences have been derived from the observations. In several instances, such as the relationship between lung cancer and cigarette smoking, the inferences have provoked considerable discussion. This in turn has led to consideration of certain selected aspects of the conceptual framework of these inferences (*1–5*). However, there still exists a need for a more general review of the methodology and of the considerations that may influence the derivation of inferences from the observations. This paper intends to provide such a review, although it does not pretend to cover all aspects of the subject. This review may give perspective on some of the issues involved. It may stimulate further discussion and investigation so that the methodological problems confronting us can be gradually resolved.

Uses and Sources of Data

Epidemiology may be defined as the study of the distribution of a disease or condition in a population and of the factors that influence this distribution. Thus, the epidemiologist is interested in variations in frequency of diseases by such characteristics as age, sex, race, social class, and occupation. This knowledge is useful for the following reasons:

1. It permits the development of hypotheses concerning etiological factors. Thus, if the disease is observed to be more frequent in a particular population segment than in others, hypotheses are developed to explain this increased frequency.

2. It can be used to test hypotheses developed in the laboratory or clinic. It is important to determine if an etiological hypothesis, based on laboratory or clinical observations, is consistent with the known distribution of the disease in human populations; to the extent that it is not consistent, the hypothesis will have to be modified.

3. It provides the scientific basis for public health administrative measures to control the disease. Even if knowledge of etiological factors is inconclusive or erroneous, epidemiological data may still be used for such control measures as case finding and the early detection of affected individuals.

The present discussion will be concerned principally with the use of epidemiological observations to elucidate etiological factors.

An epidemiological study provides data from which may be derived a series of statistical associations between a disease and various characteristics of the population. From this pattern of statistical associations, biological inferences may be drawn. The totality of the associations and the inferences constitutes the epidemiology of a disease. Thus, the epidemiological method consists of two stages: first, the

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determination of one or more statistical associations; second, the derivation of inferences or hypotheses from the series of associations.

Two distinct types of studies are used to determine statistical associations: studies of demographic data and studies of individual history data. The latter may be divided into three general categories: retrospective studies, prospective studies, and experimental studies. Of these latter, only the first two will be examined in this review. Both of these concern observations of naturally occurring phenomena, and the investigator has no direct control over other possible factors that may influence the associations so determined. Properly designed human experiments are the only certain way of establishing an association between a disease and a characteristic. However, opportunities for carrying out such studies are rare.

Demographic Studies

Demographic data are obtained principally from routinely collected vital statistics reports. They provide information concerning the distribution of either mortality or reported cases in time, by age, sex, race, social class, and other characteristics. Such data may differ from data based on individual histories in several respects. For example, demographic data may show an association between two events in time, whereas individual history data may show that an individual with a certain characteristic also has another characteristic; the latter is more likely to reflect a biological relationship. Also, certain demographic data, such as socioeconomic data, may deal with average characteristics of a group of individuals rather than with the characteristics of each individual.

Associations based on demographic data are of value in furnishing a lead for more detailed investigations. However, they must be interpreted with caution because of questions concerning the accuracy of death certification, reporting practices, and the like. General familiarity with demographic data makes further discussion unnecessary.

Retrospective Studies

The retrospective approach consists of obtaining a group of individuals with the disease, which we shall call B, and determining the percentage of these individuals who have the characteristic A, which is considered a possible etiological factor. This frequency is then compared with a similar frequency in a so-called control or comparative group of individuals without the disease. If the frequency of A is higher among those with B than among those without B, an association is said to exist between A and B. In such studies, the cases (with B) and the controls (without B) can be selected in several ways.

Hospital Populations

Most frequently, both the cases and the controls are obtained from hospital populations. Practically all the retrospective studies indicating an association between lung cancer and cigarette smoking have been hospital studies. Control groups usually consist of patients with other diseases admitted to the same hospital or hospitals. This method's popularity results from the ease and inexpensiveness with which data can be obtained. In evaluating this method, several factors must be considered and their relative importance judged by the investigator.

Probably the most frequent problem encountered in studies of hospital populations results from the influence of what is termed "selection." In this connection, it will be helpful to distinguish "sampling selection" and "biological selection." When selection is discussed in this type of study, sampling selection is usually meant. The question of biological selection will be considered later. Berkson has shown the possibility of obtaining a spurious associaciation of A and B because of sampling selection resulting from differential rates of admission to the hospital of individuals with A, those with B, and those without B (*6*). However, Berkson (*6*) and Kraus (*7*) have also indicated that if characteristic A does not influence the admission of individuals to the hospital, the likelihood of a spurious association is negligible.

Decision as to whether A does or does not influence admission to a hospital may at times be difficult. To a large extent, we are dependent on the judgment of the investigator and on our general knowledge of the specific situation, making evaluation of the results difficult. In many instances we may feel that a specific characteristic A does not influence hospitalization, but this may result from ignorance of all of the related variables involved. For example, if we are interested in determining a possible relationship between eye color and a specific disease, and we find an association between blue eyes and a disease in a hospitalized series of cases and controls, it does not appear likely that individuals with blue eyes would be selected for hospitalization. However, if we are in a community in which the ethnic group with blue eyes is predominantly in the lower social strata and if social class influences hospitalization, it is possible that sampling selection may operate to such an extent as to result in a spurious association of a disease with blue eyes.

In determining the importance to be assigned to the influence of sampling selection, another factor that must be considered is the strength of the observed association. In the extreme case, if we find that all the B individuals have A and all the non-B individuals do not have A, it would be very difficult to deny the existence of an association between A and B, unless the characteristic A exerts an unusually large influence on the chances of hospitalization. Unfortunately, most associations are not this strong. Hence, it may be helpful to judge the relative importance of sampling selection by determining arithmetically how much of an association could be expected for varying degrees of sampling selection; we shall illustrate this in our discussion of prospective studies. If the degree of the association is much greater than could be expected after taking into account what may be considered a reasonable influence of sampling selection, the association may be more readily accepted. Objections to this approach might be raised since it is not as clear cut as is usually deemed desirable. However, an element of judgment is always present in the evaluation of any set of data, regardless of the source.

In many hospital studies, confidence in an observed association may be increased by the presence of internal evidence. For example, if several non-B groups, each with a different disease or condition, are compared with the B group and the results with regard to characteristic A are similar, confidence in the existence of an association can be greater than if only one non-B group is used. Also, confidence may be greater if there is a relationship between the frequency of B and the amount of A, provided that A can be quantified. In general, the more ways in which an association can be shown, the greater can be our confidence that it is a real one and not a result of such a disturbing factor as sampling selection.

Clearly, the determination of a statistical association by hospital studies poses many difficult problems, since an interpretation concerning the existence of a relationship depends largely on the investigator's judgment regarding the plausibility of other explanations for the observed association. A point frequently overlooked is that disturbing factors actually may operate in the opposite direction so that a true association is obscured as a result of sampling selection. One might argue that this situation would occur only if the association were not a very strong one and, therefore, not very important. However, in seeking clues about etiological factors, no possible associations should be overlooked.

Controls From General Population

A modification of the hospital studies is the use of a control group selected from the general population and matched with the hospitalized cases according to certain characteristics. Usually, such a control group consists of individuals who reside in the same area and are similar in age, sex, and race to the hospitalized cases. A matched population control may diminish some of the difficulties resulting from the possible disturbing effect of sampling selection, but it is not completely clear as to how much really is accomplished. It is principally on intuitive grounds that such a control is regarded as better than a hospital control.

In some situations it is possible that a matched population control group is worse than a hospital control group. If characteristic A is another disease or condition requiring medical diagnosis for its determination, the objection could be raised that matched population controls differ from hospitalized patients with regard to the amount of medical care received. For example, in studying the association of cancer of the cervix with diabetes, we would carry out a retrospective study with hospitalized cervix cancer patients from whom we obtain a history of diabetes. A matched population control may be completely inadequate for comparison with the patients since the patients and controls would differ with regard to the amount of medical care received, and, therefore, the matched control group may actually have a larger proportion of undiagnosed cases of diabetes. This situation will arise if the information concerning diabetes is obtained by interview. However, if the presence of diabetes is determined by examination, this difficulty will not be encountered. Consequently, if it is necessary to obtain the required information by interview it may be preferable, in certain instances, to use hospitalized patients as the controls.

A control group for comparison with a hospital case group can also be obtained by selecting a random sample of the population and adjusting for differences in sex, race, age, and other variables by available statistical techniques. The question of whether to use matched or randomly selected controls has been discussed most recently by Cochran (*8*) and Greenberg (*9*). Apparently, each method has certain advantages and disadvantages, with the random sample having a slight edge. The problem of diagnostic comparability mentioned in the case of matched population controls also occurs with regard to a random sample control group.

Cases and Controls From General Population

To avoid problems imposed by sampling selection, the best approach would seem to be to obtain a sample of all cases in a community and to select either a matched or random sample of the general population as a control group. However, when samples of the general population are used, the cases and controls are again not comparable from the viewpoint of medical care. Consequently, if we are interested in determining the frequency of a characteristic that is influenced by the amount of medical care received, a more appropriate method of determining this characteristic than interviewing must be used. Selection of cases and controls from the general population appears preferable to other methods of selection in that, with this method, it is least necessary to depend on judgment concerning the relative weight to be assigned to the influence of sampling selection and other possible disturbing factors.

It is remarkable that this kind of study has not been used in epidemiological investigations of noninfectious disease more frequently than it has. The only drawback is that such studies are more difficult, expensive, and time-consuming than studies of hospitalized cases. Despite the obvious advantages, it must be admitted that theoretically this method does not avoid all possibility of sampling selection, since it might be argued that "all cases" includes only "all known cases" and undiagnosed or asymptomatic cases may have been selectively omitted with respect to the variable under study. After hospital studies have indicated the existence of associations, it would appear more profitable to expend funds and energies on confirmation by general population studies than to continue repeating hospital studies ad infinitum.

Additional Considerations

In retrospective studies, information is usually obtained by interview. Interviewing as a method of measurement has a fair amount of error, which, among other things, results in a certain amount of misclassification of individuals with and without the characteristic under study. Bross has pointed out that the ability to detect differences in the frequency of a characteristic in two groups decreases with increasing amount of misclassification (*10*). Thus, in retrospective studies, where there always will be some degree of misclassification, there is a certain risk that a true association will not be detected. This lack of sensitivity has not been sufficiently realized. In addition, the possible intrusion of subjective bias, both conscious and unconscious, must not be overlooked. When a history of a characteristic is obtained and the interviewer knows which individuals are the cases and which the controls, it is difficult to be certain that the differences observed between the two groups are not the result of subjective bias.

Retrospectively obtained data can be further evaluated by noting if the results are consistent with those obtained by demographic studies. Consistent findings will increase the confidence in the existence of observed associations, but it is difficult to determine the degree by which such confidence will or should be increased.

Prospective Studies

In prospective, or followup, studies groups of individuals with and without the characteristic A are obtained and followed for a definite period of time to determine the risk of developing B when the characteristic A is present as compared with the risk when it is absent. These groups may be selected from the population in either a random or a nonrandom manner. Several practical considerations must be taken into account in the actual process of selection. For example, if the characteristic A is very frequent in the population, a completely random sample of the population may not be the most efficient method of selecting the two groups, since the number of individuals without A in a random sample may be too small. To increase the number of individuals without A, it may be necessary to select more of them from the rest of the population by matching with the individuals with A in the random sample. A similar situation may occur with an infrequent characteristic. If we are interested in prospectively studying the association of diabetes with cancer of the cervix, it would probably be best to select a random sample of diabetic patients in the community. Then we could select either a matched control group of nondiabetics or a random sample of the entire population from which we could obtain a control group of nondiabetics by further sampling and perhaps matching. In general, the method of selection depends largely on the particular characteristics being studied.

If a nonrandom sample is used, sampling selection may be a disturbing factor. Berkson indicated this possibility in an analysis of some of the prospective studies of the association of cigarette smoking with lung cancer (*11*). In these studies, nonrandomly selected groups of smokers and nonsmokers were followed for a certain period of time, and it was observed that the death rate from lung cancer was higher among smokers than among nonsmokers. By numerical illustration, Berkson demonstrated that sampling selection may produce a spurious association. From other sources, he obtained estimates on the frequency of smokers in the population. This frequency was different from that in the study population, indicating that sampling selection had taken place. Berkson then demonstrated that this degree of sampling selection would result in a lung cancer death rate among smokers that was 1.5 times that found among nonsmokers. However, according to a report on the prospective studies by E. C. Hammond, the observed rates among smokers in the 4 age groups studied are from 3 to 17 times the rates observed among nonsmokers. For such a difference to be a result of sampling selection, it would be necessary to assume a degree of selection that apparently was not present in these studies. This example is presented to indicate the need for evaluating the strength of the association in relation to the degree of sampling selection that could have occurred. As in the case of retrospective studies, judgment must be exercised in the evaluation of the data.

The followup method of study has several advantages. First, it provides a direct estimate of the risk of developing the disease B when A is present, whereas in the restrospective method this can only be obtained indirectly. It is not certain how advantageous this really is when the major objective is to try to determine possible etiological factors. But some investigators prefer direct rather than indirect estimates. Second, a prospective study decreases the risk of subjective bias, provided that the criteria and procedures are established in advance. Third, it decreases the likelihood of misclassifying individuals with and without the characteristic. For example, in determining the relationship of artificial menopause to female breast cancer retrospectively, we are dependent on a history of artificial menopause. In a certain proportion of cases the history would be erroneous. However, in a prospective study we would start with individuals who currently have an artificial menopause; therefore, there would be no misclassification of these individuals. This tends to increase the chances of finding an association if one actually exists.

Observations to Increase Confidence

In either a retrospective or a prospective study, confidence in observed associations may be increased by including individuals who had characteristic A initially and then lost it. For example, in the studies on cigarette smoking and lung cancer, there were individuals who had been smokers and then had become nonsmokers. Therefore, it is possible not only to compare cigarette smokers and nonsmokers with regard to the risk of developing lung cancer, but also to determine the risk for individuals who were smokers and then became nonsmokers. E. C. Hammond reported that for this group the risk of lung cancer is less than for those who remained smokers. This is a valuable observation since it is less likely that such factors as sampling selection are responsible for this type of an association.

Additional confidence in the observed associations may be obtained also by comparing the affected groups and controls or those with a characteristic and without a characteristic with regard to as many other variables as possible. On the question of smoking and lung cancer, it would be of considerable interest to see if smokers and nonsmokers and if the lung cancer cases and the control groups are alike with regard to such characteristics as alcohol consumption, family size, occupation, and the like. Except for occupation, such comparisons are not yet available. This is one major methodological criticism that could be leveled at lung cancer studies. The more characteristics with regard to which the groups are similar, the more certain can one be that the difference with regard to smoking habits is real. However, the present level of epidemiological knowledge sets a limit in determining the characteristics to be selected for comparison. There is a risk of stating that the two groups are comparable with regard to characteristics that may eventually turn out to be unimportant. As knowledge of the epidemiology of a disease increases, it can be used continuously to evaluate more properly previously determined associations.

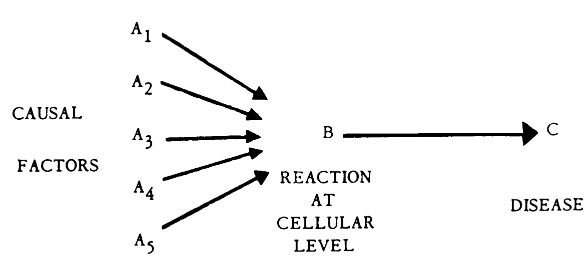
Causality in Biological Phenomena

After a statistical association has been ascertained, we would like to make some sort of an inference as to whether a cause and effect relationship exists between the disease and the associated characteristic. Before discussing factors that influence this type of inference, we need to consider the concept of causality.

In medicine and public health it seems reasonable to adopt a pragmatic concept of causality. One major reason for determining etiological factors of human disease is to use this knowledge to prevent the disease. Therefore, a factor may be defined as a cause of a disease, if the incidence of the disease is diminished when exposure to this factor is likewise diminished.

This concept is not as logically rigorous as the more formalistic one held by some investigators, which requires evidence indicating that a factor is both a necessary and a sufficient condition for a disease before it is incriminated as a cause. In biological phenomena, both these requirements do not have to be met because of the existence of multiple causative factors. For example, in tuberculosis, the tubercle bacillus is a necessary but not a sufficient condition for tuberculosis. Other additional factors included under the term "susceptibility" are important. In other infectious diseases, the micro-organism is a necessary factor but not always a sufficient one. In diseases generally considered as noninfectious, such as cancer, the concept of causation may have to be broadened further, since one particular etiological factor may not even be a necessary one because of the probable existence of multiple causative agents.

Chain of Causal Relationships



Actually, in both infectious and noninfectious diseases the differences in these two concepts of causality depend upon the frame of reference. To illustrate, the cause and effect relationships with multiple etiological factors, labeled A_1, A_2, A_3, and so forth, each acting independently, are presented in the accompanying drawing. These factors can be looked on as producing a change in B at a cellular level. The changed cell B could then develop into C, the disease. Clearly, the cellular change in B can be considered as the necessary and sufficient condition for the disease C. Therefore, to meet the more rigorous definition of causality, the biological mechanisms relating A to B and B to C must be determined. Pragmatically, however, the determination of each of the A factors is important, since attention must be focused on these to be able to apply preventive measures.

The derivation of causal inferences from observed statistical associations is difficult because of the inability to eliminate the possible effect of another variable that may influence both the characteristic A and disease B. For example, in the cigarette smoking-lung cancer relationship, it is possible to postulate the existence of another factor that causes a person to smoke and also causes lung cancer. Or perhaps there exists some constitutional factor among nonsmokers that decreases their risk of developing lung cancer. The latter viewpoint is not unreasonable since there is a tendency for persons participating in athletics not to start smoking at that time of life when smoking habits are developed. Such individuals may be constitutionally hardier as shown by their participation in athletics, and perhaps this constitutional factor decreases their risk of developing lung cancer. If such relationships exist, they would result in a statistical association without a causal relationship. This situation may be termed biological selection since individuals are selected for both the characteristic and the disease by a third mutually related factor. Similar problems are encountered in many fields, such as genetics and sociology (*12*, *13*).

Biological Considerations

One important biological consideration that may influence the derivation of causal inferences concerns the ability to experiment. If one can select samples of individuals from a population and randomly allocate them to two groups, one with and the other without the characteristic, and the statistical association continues to exist, the randomization procedure has taken into account most, if not all, of the other related variables. Such well-controlled experiments had a major role in establishing a causal connection between fluorides in drinking water and reduction in dental caries. However, experimentation is not usually feasible in most human diseases.

Another influential factor is the degree of the observed association. If the statistical association is very strong, it is less reasonable to suppose that a mutually correlated third factor was involved. Admittedly, a 100 percent association does not completely eliminate the possible existence of a third factor, but it does make such a possibility more unlikely. Here again, such a situation is rarely encountered.

Probably the most important consideration is whether or not the association is consistent with existing biological theory. If a statistical association makes biological sense, it is more readily accepted than one that is at the moment not capable of biological explanation. By "biological sense" we mean that the mechanisms leading from the characteristic A to the disease B fit into some biological (physiological or pathological) framework. If this framework exists, it was probably derived from other kinds of observations; therefore, it is intuitively felt that the association has been verified by other, independent observations.

This type of reasoning can be illustrated from studies of pregnancy experience and neuropsychiatric disorders in childhood (*14*). In these studies an association was demonstrated between certain maternal factors during pregnancy and the development of such disorders as cerebral palsy, epilepsy, and mental deficiency in the offspring. This association fits into a reasonable biological framework since the mechanisms of such relationships are readily conceived. These same factors have been shown to produce anoxia in the fetus, and anoxia may result in damage to the brain, which, in turn, is logically related to the disorders mentioned. Consequently, the statistical association is readily acceptable as a causal hypothesis.

On the other hand, in the association of cigarette smoking and lung cancer, no direct links between cigarette smoking and cancer have been worked out. There is evidence indicating that environmental agents are important in the etiology of cancer, which does strengthen the hypothesis that cigarette smoking and lung cancer are causally related. It also seems more reasonable to accept cigarette smoking as a causal factor than the application of a certain ointment to one's feet or the ingestion of alcohol, since cigarette smoke does come in contact with the site of lung cancer. But the biological plausibility of a causal hypothesis on these two bases is not of the same order as in the case of pregnancy factors and neuropsychiatric disorders.

There are historical instances in which a statistical association did not originally conform to existing biological concepts. As advances in knowledge changed the biological concepts, these new concepts were found to be consistent with the previously observed association. Conversely, there have been instances in which the statistical association was interpreted as being consistent with existing biological concepts, but later the interpretation of the association was found to have been erroneous.

The classical example of the first situation is afforded by Snow's investigation of cholera (*15*). Snow observed an association between the ingestion of polluted water and the development of cholera during 1849–54. At that time, prior to the establishment of the germ theory of disease, the accepted etiological hypothesis for cholera was the miasmatic theory. Snow's observations were not generally accepted since they did not conform to the miasmatic theory. After the germ theory of disease was established, Snow's statistical association was consistent with the germ theory, and, hence, it was accepted. Thus, the prevailing biological opinion was erroneous whereas the inference made from the statistical association was not.

The second situation is exemplified by Farr's observation of an association between elevation of residence above sea level and cholera mortality in London (*16*); his data, for 1848–49, are shown below. With increasing elevation, there was a decline in cholera mortality. This association was consistent with the miasmatic theory and was interpreted as confirmatory evidence. When the miasmatic theory was replaced by the germ theory, this association was still reasonable since elevation was in turn inversely associated with the etiological factor, polluted water.

Elevation above sea level, in feet	*Deaths in 10,000 inhabitants*
Under 20	102
20–40	65
40–60	34
60–80	27
80–100	22
100–120	17
340–360	7

One other biological consideration is the role of animal experimentation. There is a widespread feeling that, if a statistical association is confirmed by an animal experiment, definite proof of a cause and effect relationship in humans is established. It is important to realize that applications of the results of animal experiments to human situations are fraught with danger. If we are concerned with such disturbing influences as sampling and biological selection in studies of humans, we should be so much the more careful of basing conclusions on results of animal experiments. Confirmation by animal experimentation increases the biological reasonableness of a causal inference. It also provides an animal model by which possible biological mechanisms may be elucidated, thereby indicating how and where such mechanisms might be investigated in humans. But, in interpreting results from animal experiments, it is important to distinguish between definite proof and increased biological plausibility.

Nonbiological Considerations

Certain nonbiological considerations may influence an individual's attitude toward acceptance of a causal inference. These concern the decisions that are made relative to the course of action to be taken when an inference is accepted. They reflect the outlook, background, and administrative responsibilities of the individual. For example, a research scientist, without any direct responsibility for the health of a population, might require a very high degree of plausibility before accepting a causal inference and recommending definite administrative action. On the other hand, a health officer, directly responsible for the health of a population, may accept a lower degree of plausibility as sufficient to warrant preventive action. He may therefore accept a causal inference when he thinks that it has a good chance of being correct but before it is definitely proved.

Such considerations usually play a role after the statistical association is established and before a causal relationship is definitely proved. During this period, causal inferences are regarded with varying degrees of plausibility. It is helpful to consider the possible relationships between courses of action and degrees of plausibility, as follows: At the first level, the evidence is considered sufficiently suggestive to warrant further investigation. At the second level, the evidence is considered sufficient for recommending attempted preventive action. At the third level, the evidence is considered sufficient to state that a causal inference has been proved, and this causal hypothesis is included in our body of scientific knowledge. There is an interaction between the degree of plausibility with which an inference is regarded and the actions based on these inferences.

It seems that the present controversy over the inferences from the cigarette smoking-lung cancer association is largely concerned with the degree of plausibility. It is generally agreed that the evidence is sufficiently suggestive to warrant further investigation. At the other extreme, there is general agreement that the evidence is not sufficient to warrant a statement that a causal hypothesis is definitely proved; this level will not be reached until the detailed biological and chemical mechanisms have been worked out. At present, the major issue is whether a causal inference is sufficiently plausible for a public statement that cessation of cigarette smoking would diminish the risk of acquiring lung cancer. Since the degree of plausibility cannot be directly assessed, differences of opinion naturally develop.

In evaluating these decision levels, it is important to keep in mind that in many instances action based on a statistical association could be successful even though it is interpreted incorrectly from a biological viewpoint. To illustrate this we recall Farr's observation of the association of decreasing cholera mortality with increasing elevation of residence above sea level (*16*). If the health officer had recommended that people living in the lower-lying districts of London move to the higher districts, a decline in cholera mortality would probably have resulted, although such action would have been based on the erroneous miasmatic theory.

Summary

Increasing use of the epidemiological approach in the study of noninfectious diseases emphasizes the need for considering the conceptual framework of such studies. Epidemiological studies are composed of two stages: first, the determination of statistical associations between a disease and various population characteristics; second, the derivation of biological inferences from the pattern of associations. Both the associations and inferences constitute the epidemiology of the disease.

Statistical associations may be determined from demographic data or from individual history data. The latter may be obtained from retrospective studies, prospective studies, or experimental studies. In these studies, characteristics of a group of cases are compared with those of one or more groups of controls. Cases and controls may be selected by various methods, each of which has advantages and disadvantages.

In general, leads to the existence of statistical associations come from individual history studies of hospital populations or from demographic data. The associations so suggested require confirmation by retrospective studies of adequately selected samples of cases and controls from their respective populations. Whether or not prospective studies are necessary depends largely on the kind and strength of the association. The method of carrying out a prospective study depends on the nature of the characteristics and the disease under investigation.

In the derivation of causal inferences from observed statistical associations, certain biological and nonbiological factors are influential. Among the biological factors are the ability to conduct human experiments, the strength of the association, the role of animal experimentation, and the prevailing biological concepts. The latter is the most important. Snow's and Farr's observations on cholera are illustrations of the interaction between biological theory and the interpretation of statistical associations. A nonbiological factor is the course of action resulting from the degree of plausibility with which a causal inference is regarded. This factor, directly or indirectly, influences an in-

dividual's basic way of thinking about causal relationships.

We hope that this brief review of some of the methodological and inferential problems encountered in epidemiological studies will stimulate further discussion. There exists a compelling need for establishing some general principles which would provide a logical framework for future investigators.

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CDC Course in Epidemiology for Nurses

A refresher course for nurses in communicable disease control will be given by the Communicable Disease Center, Public Health Service, Atlanta, Ga., from April 8 through April 26, 1957. The course is open to public health nurses and educational directors, industrial nurses, and instructors and consultants in nursing.

Designed to increase nurses' technical knowledge and skills in the prevention and control of communicable diseases, the course will stress epidemiological principles and techniques.

Supervised practice in the field may be arranged for a limited number of students after the termination of the course.

Applications must be filed with the Communicable Disease Center by March 10, 1957. Information and application forms may be obtained from the director of public health nursing in a State health department or from the Chief, Nursing Section, Epidemiology Branch, Communicable Disease Center, Public Health Service, 50 Seventh Street, NE., Atlanta, Ga.