Carrying the same warning against the pseudoscientific method that applies to cancer epidemiology, this message is broadened to the whole field of noncommunicable diseases by an epidemiologist who knows the pitfalls.

Epidemiology in Noncommunicable Disease

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WHENEVER public health interest is newly attracted to a disease, one commonly hears it said "We must do some epidemiology on it." This is a pious idea, and all who class themselves as epidemiologists would concur in it. However, even among epidemiologists there would probably be little agreement on the important details of what constituted "doing some epidemiology" and even less agreement on what one might expect to learn from "doing it." It is not proposed here to attempt to outline a practical blueprint one might follow in doing some epidemiology. It would, however, appear to be useful to organize some ideas as to the stuff of which most present epidemiological evidence in noncommunicable disease is made and discuss some of its potentialities and limitations.

"Upon the People"

As not a few of us are aware there are probably as many definitions of epidemiology as there are people classed as epidemiologists. Except for those definitions that are patently wrong, even as applied to communicable diseases, like the one found in the second edition of Webster's unabridged dictionary, all have as their central idea the study of disease in human populations for that aid which knowledge gained may give in determining factors related to, or governing, disease occurrence. All medical sciences have this objective—determination of etiological factors. Epidemiology, which is derived from Greek roots meaning "upon the people," differs most essentially from other disciplines in that its universe of study is human society or selected segments of it, rather than the individual.

For the purposes of this discussion epidemiology may be divided into two broad branches—descriptive and determinative. Descriptive epidemiology, through studies in human populations, concerns itself with characterizing or describing the kinds of people who acquire or escape disease. Determinative epidemiology tests in human experience inferences drawn from the evidence of descriptive epidemiology or from other bodies of knowledge. Following the working definition just mentioned, descriptive epidemiology enumerates factors related to disease; and determinative epidemiology attempts to define those which govern its occurrence. Though all factors governing disease occurrence are related to it, the converse is not always true, for factors associated with disease do not necessarily govern its occurrence.

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Thus, endemic pellagra in southern mill villages was firmly associated with a diet of corn bread, fatback, and blackstrap molasses although this diet was not the direct cause of the disease.

Measuring Risk

In characterizing the kinds of people who acquire and escape disease, the initial effort of descriptive epidemiology is to measure risk in groups of people with different characteristics. Risk is measured through computation of incidence, which is an expression of the probability that one of a group will develop or die from disease in a period of time. It should not be necessary to define the word "incidence," but it is appropriate to do so since it is so badly misused in the literature of clinical medicine and pathology—the literature which comprises much of present epidemiological evidence in noncommunicable disease. Since data are so often labeled "incidence" when they may not even reflect it and conclusions then drawn which would be valid only if the data did in fact represent it, an agreement on its meaning is more than a question of semantics.

Three elements enter into the computation of incidence: the population at risk; all cases or deaths occurring in the population; and a specified period of time. Incidence is thus the rate of occurrence or diagnosis of disease, or death, per unit of general population during a period of time. In this country, at least, it is becoming most acceptable practice to limit the use of the word to morbidity data—an expression of rate of occurrence or diagnosis of disease. It is still, however, in conformity with good usage to apply the term to death data. Although there is abundant precedent in reputable medical literature for using the word "incidence" in describing data other than those representing probability of occurrence of disease, such misuse is in large part responsible for a great deal of present confusion in epidemiological evidence pertaining to many noncommunicable diseases. It is not infrequent to see the word applied to as many as four totally different kinds of data in the same medical article. Because of this practice, it is necessary to be quite wary every time the word is encountered. Cursory examination of presented data will frequently reveal that they do not represent true incidence, and thus are not measures of risk although the author draws conclusions which would be valid only if they did so in fact.

Descriptive epidemiology employs two general methods in attempting to measure risk to disease in groups of people with different characteristics. These may be called the direct, or population method, and the indirect, or case history method. These methods differ not only in the detailed procedures they employ, but more importantly in the confidence which may be placed in evidence derived through their use.

Indirect or Case History Method

The time-honored but less satisfactory technique in measuring risk is the indirect or case history method. By case history method is not meant the detailed study of a single case although such study has a definite place in some epidemiological investigations. The case history method is here intended to mean the procedure which has as its point of departure records of a group of cases of a disease. It has been employed by astute clinicians and pathologists ever since formal or informal summaries of series of cases have been made. Characteristics of patients are obtained through observation or interview of individuals. Histories obtained are compared with those from a control group of well people or with patients from the same clinical experience who have presumably unrelated disease. Risk to the disease under study is inferred from differences demonstrated between study and control groups.

In the earliest application of case history method, the kinds of patient attributes available for study were those recorded in connection with clinical care. These included such characteristics as age, race, sex, marital status, occupation, family history of disease, place of residence, and others. As associations between such characteristics and a disease were suggested in a small series, or from one locality, similar observations were extended to larger series and to other localities. Associations so derived which offered some plausible explanation for disease causation were then further tested in a larger series for the purpose of getting detailed information on the particular attribute. To obtain a large enough series so

that statistical significance might be attached to associations developed, recourse was generally had to large general hospitals in which a substantial number of patients with the disease might be anticipated. Or, questionnaires for completion were submitted to a number of widely scattered physicians specializing in the disease so that a substantial number of records might be analyzed. While satisfying the need for numbers, these procedures sacrifice the more essential necessity for interview of cases which are truly representative of the disease in general. When, however, great care is taken in selection of patients and controls for interview, the purposeful questionnaire represents the case history method at its best. Some mention will be made later about the security of the evidence derived from it.

There are several other minor modifications of what is here called the case history method. Instead of using a series of cases, as outlined above, to enumerate attributes or history which are associated with a disease, these cases have been used in attempting to reflect incidence of disease in some locality; incidence among some occupational group, or in some race; or as indicators of disease trends. This variant deserves some mention since, in the literature of pathology and of clinical medicine, it is so commonly employed in an effort to measure risk to a large number of noncommunicable diseases. It is regarded as particularly appropriate for diseases which require special skills in their diagnosis: skills that are generally found only in well-staffed hospitals. Since the diagnostic court of last resort is the autopsy table, some regard as valid only that evidence derived through analysis of necropsy series.

In principle this variant consists in taking admissions to a hospital, disease or deaths occurring in some closed population such as employees in an industry, or autopsies performed in a hospital, and computing the percentage that the disease under investigation is of the total. Thus, it is noted in one South African hospital that primary cancer of the liver is found in 90 percent of cancer autopsies among Bantu, while only 1 or 2 percent of cancer found at autopsy among Europeans is at this site. Ergo, the "incidence" of primary cancer of the liver is from 45 to 90 times greater in Bantu than in Europeans. Or, respiratory cancer comprises 30 percent of all cancer deaths observed in employees of a certain industry, while only about 15 percent of all cancer mortality in United States males is at this site. Ergo, employees of this industry suffer an "incidence" of respiratory cancer which is twice that observed in all males. Or, in General Hospital X, 20 years ago 4 percent of all cancers found at autopsy were charged to carcinoma of the lung while now this site comprises 11 percent of the total. Ergo, the "incidence" of carcinoma of the lung has nearly trebled in 20 years.

Examples of evidence of this type may be found in the literature of all noncommunicable diseases. The authors almost invariably label as incidence the ratio of one disease to the total. Such ratios in fact, however, are relative frequencies and cannot even be assumed to reflect incidence, much less measure it, unless a number of other conditions are satisfied. Unless all illnesses occurring in a definable population are diagnosed in the hospital, or unless they comprise a sample of known composition, relative frequencies computed from hospital data cannot be assumed to reflect incidence of disease in the population the hospital serves. The situation with regard to autopsies is even worse since selective factors, additional to those which bring the patient to the hospital in the first place, operate in determining which fatal case is autopsied. Autopsies in most hospitals thus represent a sample of a sample of an unknown amount of illness occurring in a population of unknown composition. No one has yet devised a practical, uniform way to compute incidence from data of that kind.

The practice of using hospital or autopsy series in an effort to measure risk to a wide variety of diseases, among people possessing greatly different characteristics, stems from the constant search of the epidemiologist for significant differences in risk. If the Bantu do in fact suffer an extraordinarily high risk to primary carcinoma of the liver, then a number of hypotheses are suggested, and there is real hope that further epidemiological research may contribute to a knowledge of the essential causes of this disease. The enormous diversity in race, environment, nutrition, social customs, and a host of other factors available to us in the life

experience of different peoples throughout the world need no emphasis. Utilization of these differences in describing factors related to any disease, however, requires that risk to disease be measured in the groups possessing different characteristics. This cannot be accomplished directly through relative frequencies derived from routine hospital and autopsy experience. To make full epidemiological use of the obvious differences between, say, South African Bantu and American Negroes requires first that a real difference in risk to disease be demonstrated. If some uniform and practical way can be found to accomplish this through use of hospital and autopsy statistics, then the potentialities of the epidemiological method will be greatly enhanced. In spite of the fact that no practical solution is obvious and in spite of the opinion held by many that none is possible, one should not be deterred from seeking a practical way to make such data valid reflectors of risk.

Population or Direct Method

The population or direct method of measuring risk has as its point of departure a group of people instead of a group of cases of disease. The population under study is generally selected because it is known to possess general or specific characteristics which set it apart from the universe of which it is a part, or because it is different from some other distinct group. Or, an entire population may be divided into those who possess or lack characteristics of interest. Disease occurrence is then measured in the segments with different characteristics. In some instances disease occurrence may be measured in retrospect, but preferably the population is first characterized and subsequent occurrence of disease in the subgroups with different characteristics is measured by means of a study projected into the future.

The bulk of the evidence of descriptive epidemiology which is presently available for noncommunicable diseases has been derived through applications of some variant of the case history or population methods of study. For most of these diseases by far the largest proportion of the evidence has been acquired through case history investigation.

Security of Case History Evidence

The confidence which may be placed in case history evidence obviously varies with the disease under study. It also varies with the characteristic or history under investigation, particularly in relation to the likelihood of its being remembered and divulged with equal accuracy by cases and controls. In addition, the security of case history evidence depends heavily upon selective factors which determine the representativeness of the samples of cases and controls which are interviewed. It is not too difficult to make them representative with regard to such factors as age, race, sex, and residence. Until information is accumulated about all of the important characteristics associated with the disease, however, one is unable to estimate accurately just how representative the sample is. For example, the recently accumulated evidence for an association between cigarette smoking and carcinoma of the lung, at the very least, means, that in future studies of lung cancer, stabilization of smoking habit patterns is just as important as stabilizing such factors as age, race, sex, and residence.

All of these considerations have an important bearing on any estimate of the security of case history evidence, and the three factors mentioned are by no means all which bear on it. It is, therefore, best to accept case history evidence with reserve. In this sense, characteristics of patients enumerated by the case history method should be looked upon as having an initial validity about comparable to that of the clinical impression. The clinical impression is invaluable in providing concrete leads and points of departure for further investigation. It should not be regarded as fact until sufficient replication and direct and indirect verification attest to its consistency.

Associations and Hypotheses

It should also be remembered that even after an association between some disease and a patient attribute has been fully established, it does not necessarily follow that this attribute is an essential cause of the disease. As mentioned previously it is now known that neither low income nor a diet of corn bread and blackstrap had any direct role in causing pellagra, although

there was a high degree of association between these patient attributes and the disease as it occurred in the southern United States.

Associations, no matter how they are derived, do suggest hypotheses. Hypotheses which can be subjected to further test serve a useful purpose. But until they are adequately tested, no useful purpose can be served by parading them as fact.

In selecting the phrase noncommunicable disease for this discussion, it was not intended to imply that the large body of diseases now regarded as noncommunicable are necessarily so in fact. Impressed as we are with the skill and accomplishments of the microbiologist, we are apt to regard failure to identify some infectious agent as proof of noncommunicability. Communicability, however, is not fundamentally a concept of microbiology. It is a function of behavior of disease in human populations and, as such, is an epidemiological concept. For example, in spite of its microbial origin, it is known that tetanus is not communicable because of the way in which it is distributed in people. While it is highly unlikely that any disease would be seriously regarded as communicable today unless an agent had been identified, it should not be forgotten that the basic evidence for communicability lies not in microbiology but in behavior of disease in human populations.

In considering evidence which might bear on communicability it should also be remembered that infectious diseases vary in both their frank and apparent contagiousness. That chickenpox and measles are "catching" is obvious to laymen. Paralytic poliomyelitis frequently appears less so than an outbreak of broken legs. Brill's disease, while not communicable in the ordinary sense, has now been shown to represent a manifestation of infection acquired many years before—it has a very long latent period, as does leprosy. Clinical manifestations of tuberculous infection depend to some extent on the age at which infection is acquired. Thus, there is enough analogy with known infectious processes to warrant asking if some so-called noncommunicable disease might actually be communicable in spite of absence of obvious evidence for it.

In the literature of cancer there is very little epidemiological evidence that bears on this question in more than a superficial manner. For example, surgeons and gynecologists, who are exposed to many "open" cases, apparently have a lower risk to cancer than other specialists who are not heavily exposed in their practice. On the other hand, there is an abundant literature illustrating familial aggregation of the disease not dissimilar to that found in the older literature of tuberculosis.

It is tempting to argue by analogy with known infectious processes and attempt to explain some of the evidence on the basis of an infectious origin of cancer, but no useful purpose is served by doing so. The present scientific dictum that cancer is not communicable makes good sense and is entirely consistent with evidence now available. It should be recognized, however, that on the basis of present epidemiological evidence this is essentially a dictum. Neither dicta nor voices of authority should overawe or deter us from collecting and examining pertinent epidemiological evidence which may bear on whether many diseases now quite properly regarded as noncommunicable are so in fact.

Refinement in Measurement

Before closing this discussion there are several other considerations which deserve mention. As all who have attempted epidemiological studies are aware, one of the primary deterrents to effective use of the method is inherent in the difficulties encountered in dividing any general population into those who do and those who don't have the disease under study. This difficulty naturally varies with the disease but in all diseases has two general components. The first part of the difficulty depends upon the ease with which the disease may be accurately diagnosed and the second, on the ease one might expect to have in counting cases once they are clinically identified.

Precision of diagnosis depends in large measure on the kinds and availability of diagnostic skills and techniques necessary for effective identification of disease. If the disease in all of its stages can be accurately diagnosed by the average practitioner on clinical grounds,

then no difficulty is encountered. On the other hand, if specialist-care, hospitalization, laboratory procedure, or autopsy is necessary, then one must expect that a number of cases will go unrecognized. Further, the selective factors leading to the recognition of the few will be generally unknown. Between these extremes, all gradations of difficulty in diagnosis are encountered among the noncommunicable diseases.

The only direct and completely satisfactory solution to the general problem of case identification depends upon the development of inexpensive and objective diagnostic tests which are practical for application to the general population. Although this has been the experience in communicable diseases, extremely useful, epidemiological study did not have to await such tests. The problem may be looked upon as one of refinement in measurement. While one would like to have the diagnostic precision obtained by the autopsy, the diagnosis possible from clinical examination by the average practitioner has important epidemiological uses. All science seeks to measure on an increasingly fine scale. On a relative scale, if the autopsy represents diagnostic measurement to the nearest millimeter, then the death certificate in some areas might record only the nearest mile. While a millimeter scale is desirable, a mile stick is a useful device provided it is clearly understood that it is a mile stick and not a millimeter stick. If so much enthusiasm were not exhibited in the belief that hospital autopsies measure incidence, a way might be found to use necropsies to calibrate the death certificate in the area the hospital serves.

Once cases are identified the problems involved in counting them also vary with disease. For those which produce symptoms of the kind and severity which lead patients to medical care, there are many devices which have been employed in estimating their number and location. In some diseases, however, such as certain types of mental deficiency, the seeking of medical attention is frequently dependent entirely upon social and economic factors and bears little relation to the illness itself. Some may not even be detected in a careful survey because of a tendency of families to hide them. More than ordinary ingenuity is required in counting cases such as these.

Difficulties attendant upon counting cases of noncommunicable diseases have led many to recommend establishment of case registers. If experience in cancer is any guide this effort is generally unsatisfactory. Case registers for epidemiological purposes require competent statistical design and close technical supervision in their operation. They are also expensive. Of the many cancer registers established in this country there are only two which meet more than very superficial epidemiological needs, although many may serve some other laudable purpose, such as directing attention to particular needs in a service program. As most cancer registers operate in practice, however, the cases recorded are generally as unrepresentative of all existing cases as are those cases which gravitate to some particular hospital.

Some attention is being given the idea of establishing a few selected areas for general morbidity reporting. This deserves further consideration since the expense in terms of technical skills and money is not increased in direct proportion to the number of diseases included. The adequacy of communicable disease reporting has generally been a direct function of the service provided patients and their physicians as a result of the report. Physicians may be expected to cooperate generally with noncommunicable disease reporting if they can be shown that something worthwhile will come of the effort.

Until adequate access can be had to noncommunicable disease as it occurs in definable populations, substitute procedures for estimating their number and characteristics will continue to be employed. Because large general and specialized hospitals provide ready access to competently diagnosed cases, as well as autopsies, the case history method will continue to be applied to them. There is a general tendency of the professional epidemiologist and the biometrician to be scornful of the efforts of the clinician and pathologist in this direction. While a critical attitude is justified, a scornful one contributes nothing constructive. The fact that no practical way seems possible to make this readily available material of more general

epidemiological usefulness merely increases the challenge to those with the technical skills which might contribute to a solution.

At the beginning of this discussion the question was inferred "what might one expect to accomplish in 'doing some epidemiology' in noncommunicable disease?" As far as the past is concerned, epidemiology has made substantial contribution in some. For example, all of the knowledge essential to practical control of both mottled enamel and pellagra was acquired through application of epidemiological method. As to the future, descriptive epidemiology alone, as a minimum, should direct attention to those segments of the population in which greatest returns from "control" measures might be expected. Aside from that, one can only say with assurance, that from whatever scientific discipline the clues to etiology of disease eventually come, they will remain unacceptable until they have stood the test of consistency with epidemiological facts—consistency with the facts of occurrence of disease in human populations.