Epidemiology

Principles and Methods

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Preface

The objective of this book is to introduce the principles and methods of epidemiology, particularly as they are applied in the study of those chronic diseases for which preventive measures are now unknown or inadequate. The book began as a new edition of *Epidemiologic Methods,* published ten years ago, but, as we contemplated a revision, it seemed to us preferable to write a new book emphasizing principles as well as methods, giving more consideration to the historical roots of epidemiology and dealing somewhat more broadly with the interaction of genetic and environmental factors in the etiology of disease. Methodologic approaches that have seen important developments in the last decade—notably studies of migrant populations and the detection of low-intensity disease clustering—have been included.

There is, at the present time, considerable concern over the possible effects on human health of environmental contaminants. It is evident that much more knowledge of the long-range effects of these substances must be obtained. In that this book's major emphasis is on the elucidation of cause-effect relationships, it has relevance to this problem.

The study of chronic disease epidemiology is inconceivable without knowledge of biostatistics. Elementary statistical techniques are essential to our subject. However, because accounts

of these techniques appear in many textbooks of biostatistics, we have avoided the repetition of such material. It is also evident that biostatistics is providing some of the most important methodologic advances in epidemiology. Detailed accounts of these more advanced statistical methods are also not included, since we have attempted to produce a book that is intelligible to a person with medical or biologic, but not necessarily statistical, training. For this reason, the book should be considered an introduction to chronic disease epidemiology rather than a comprehensive account of the subject.

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Acknowledgments

The difficulty of defining accurately the sources of one's ideas, points of view, and information is well known. This book has been influenced by the thoughts and efforts of so many colleagues and students that to most of them we can offer only this general acknowledgment of our indebtedness.

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Epidemiology

DEFINITION

Epidemiology is the study of the distribution and determinants of disease frequency in man.

Two main areas of investigation are indicated in this definition—the study of the *distribution* of disease and the search for the *determinants* of the observed distribution. The first area, describing the distribution of health status in terms of age, sex, race, geography, etc., might be considered an extension of the discipline of demography to health and disease. The second area involves explanation of the patterns of distribution of a disease in terms of causal factors. Many disciplines seek to learn about the determinants of disease; the special contribution of epidemiology is its use of knowledge of the frequency and distribution of disease in populations.

Like many sciences epidemiology has developed from the study of the exotic and the unusual into the elucidation of general principles. Epidemiology is now no more restricted to the study of striking outbreaks of disease than meteorology is to the study of hurricanes or astronomy to eclipses of the sun. Yet an epidemiologist might today still consider his concern to be primarily the study of epidemics, if a broad view is taken as to what

constitutes an epidemic and if it is recognized that research designed to explain epidemics cannot be restricted to periods during which the epidemics prevail.

Concept of an Epidemic

In the past the term *epidemic* was used almost exclusively to describe an acute outbreak of infectious disease. More current definitions stress the concept of *excessive prevalence* as its basic implication in both lay [132] and professional [13] usage. This characteristic is exemplified by many noninfectious diseases as well as by diseases known to be associated with microorganisms. The United States, for example, is at the present time in the grip of epidemics of at least two seemingly noninfectious diseases—coronary atherosclerosis and lung cancer—which easily satisfy the criterion of excessive frequency. Lung cancer is now over 30 times more common in this country than it was 50 years ago; coronary heart disease accounts for nearly one-third of all deaths in the United States, although there are areas of the world where it is relatively infrequent. In noninfectious, as in infectious, diseases the idea that the frequency of a particular disease is excessive may be gained by following its frequency over time, by comparing its frequency in different places, or by comparing one subgroup of the population with another. That the excessive frequency must come about within a period as short as a few days or weeks is no longer considered an essential part of the meaning of epidemic.

Epidemic and Nonepidemic Frequency

Even when the predominant concern is the explanation of epidemics, knowledge of disease frequency and distribution during nonepidemic times may be crucial. There are several bases for this.

1. Without knowledge of nonepidemic frequency, how can the existence of an epidemic be demonstrated? How can it be determined that the frequency of a disease in a particular population at a particular time is in excess? Clearly it is necessary to know the frequency of the disease in other populations and in the same population at other times.

Sometimes the existence of an epidemic is obvious. This is so when the epidemic involves a large number of persons, produces a distinctive illness, and occurs over a short period of time. Thus there is little difficulty in detecting epidemics of cholera, plague, smallpox, or the common infections of childhood. In all these the disease is familiar, the difference between epidemic and nonepidemic prevalence is large, and the transition is rapid. In contrast, the risk to an American male of dying of coronary heart disease is currently quite as large as the risk of death experienced during some of the major historical epidemics of infectious disease, yet the general population remains almost unaware of the existence of an epidemic of coronary heart disease. The slow growth of this epidemic has concealed its size.

Even acute epidemics may pass unnoticed if they appear in unfamiliar form. For example, during the intense London fog of 1952 there was very limited realization of the effects of the fog on the population's health. The full effect was appreciated only when deaths for the period were counted (Fig. 1) and compared with deaths during the preceding and subsequent periods of the same year and during similar periods of previous years. It then became apparent that the fog had been responsible for over 4000 deaths.

2. An unusually low disease frequency in a population may be just as significant in understanding the causes of epidemics as a high frequency. For example, the very low attack rates from cholera observed by John Snow [376] among two groups of people (workers in a brewery and denizens of a workhouse) in the center of an otherwise epidemic area led to a strengthening of the belief that the water supply was responsible for the epidemic since these two groups did not share the general water supply of the neighborhood. Similarly, the virtual absence of cancer of the uterine cervix in nuns is an important consideration in the formation of hypotheses regarding the etiology of this disease.

3. In the chronic diseases, which have prolonged upswings and downswings of the epidemic wave, it may be difficult to decide whether or not a given frequency qualifies as epidemic (or excessively prevalent) even if all the necessary comparative information is available. It is common to find a gradient in the frequencies of a disease in different populations. While the dis-

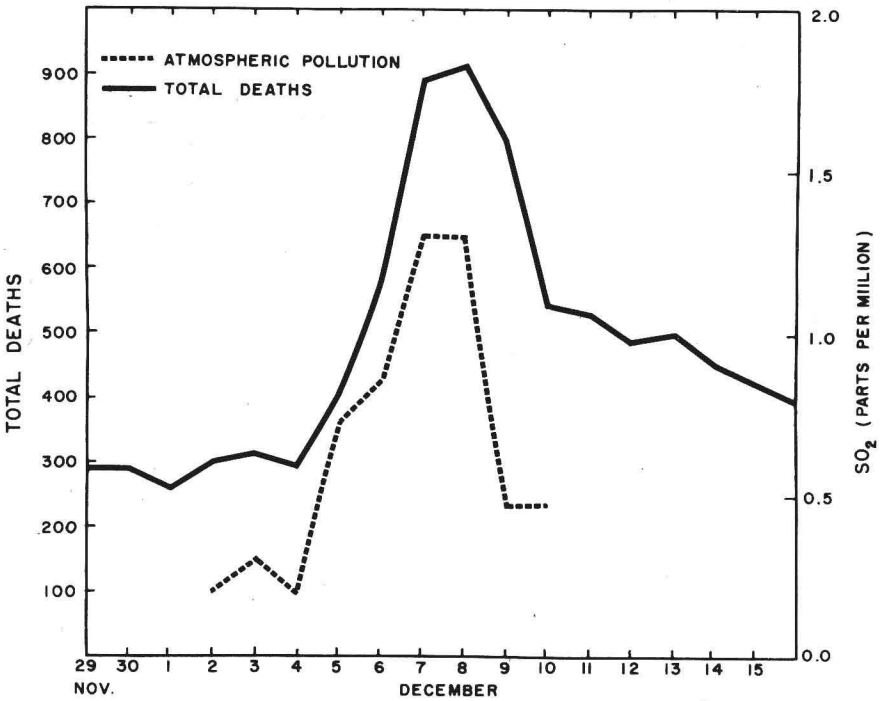

Figure 1

Atmospheric pollution (parts per million of sulfur dioxide) and numbers of deaths per day in London, Nov. 29 to Dec. 16, 1952. (Data from a report of the Ministry of Health [257].)

ease may be considered definitely epidemic when populations with the highest frequencies are compared with those with the lowest rates, the applicability of the term to populations with intermediate frequencies will depend largely on the observer's point of view. Under such circumstances attempts to correlate quantitative statements of disease frequency with quantitative statements of the frequency of the suspected factors are more revealing than attempts to correlate the dichotomy of epidemicity and nonepidemicity with the dichotomy of presence or absence of specific factors.

HISTORICAL BACKGROUND

Some of the basic concepts underlying the practice of epidemiology can be illustrated by reference to historical episodes and

personalities. A few episodes which seem particularly relevant to the development of current concepts and methods—as distinct from substantive knowledge of the epidemiology of particular diseases—are outlined in this section. While in one sense epidemiology is almost as old as medicine itself, in another sense it is a very new discipline. Although Hippocrates spoke in terms that have meaning to epidemiologists today, it is only in the last few decades that epidemiology has become recognizable as a named discipline with which investigators, research groups, and academic departments are identified.

The history of epidemiologic methodology is largely the history of the development of four ideas: (1) human disease is related to man's environment; (2) the counting of natural phenomena may be instructive; (3) "natural experiments" can be utilized to investigate disease etiology; and (4) under certain conditions, experiments on man can also be utilized for this purpose.

Disease and Environment

The idea that disease may be connected with a person's environment was expressed by Hippocrates almost 2400 years ago. Today the concept seems self-evident, but the clarity of his statement, and its relevance to the objectives of epidemiology today, deserve recognition. In *On Airs, Waters and Places* [163] Hippocrates states:

> Whoever wishes to investigate medicine properly should proceed thus: in the first place to consider the seasons of the year, and what effects each of them produces. Then the winds, the hot and the cold, especially such as are common to all countries, and then such as are peculiar to each locality. In the same manner, when one comes into a city to which he is a stranger, he should consider its situation, how it lies as to the winds and the rising of the sun; for its influence is not the same whether it lies to the north or the south, to the rising or to the setting sun. One should consider most attentively the waters which the inhabitants use, whether they be marshy and soft, or hard and running from elevated and rocky situations, and then if saltish and unfit for cooking; and the ground, whether it be naked and deficient in water, or wooded and well watered, and whether it lies in a hollow, confined situation, or is elevated and cold; and the mode in which the inhabitants live, and what are their pursuits, whether they are fond of drinking and eating to excess, and given to indolence, or are fond of exercise and labor.

In light of this clear and firm admonition from such an influential teacher, it is remarkable that virtually nothing was discovered about the specific characteristics of unhealthy environments during the subsequent 2000 years. Greenwood [135] attributes this to the fact that the operative word in Hippocrates' statement was *consider*—not *count*. However full of insight an investigator's considerings may be, they are unlikely, if not supported by observations objectively recorded in quantitative terms, to form a basis for the considerings of successive generations of investigators.

Counting and Measurement

The introduction of quantitative methods to epidemiology—indeed, to biology and medicine in general—is credited to John Graunt, who in 1662 published his *Natural and Political Observations . . . on the Bills of Mortality* [134]. Graunt analyzed the weekly Bills of Mortality and the parish registers of christenings in London during the previous decades, noting the excess of males over females among births and deaths, the high rate of mortality among infants, seasonal variation in mortality, and many other features of birth and death data. He provided a numerical account of the impact of the plague on the population of the city and examined the meteorologic and other ecologic characteristics of the years in which plague struck. He made pioneering attempts at two basic biostatistical procedures—the estimation of population and the construction of a life table. More significantly, however, he demonstrated "the uniformity and predictability of . . . biological phenomena taken in the mass" [418] and thus is widely regarded as the founder of the science of biostatistics. Since these new techniques saw no further epidemiologic application for almost 200 years, Graunt might more appropriately be regarded as a forerunner than a founder of epidemiology.

"Natural Experiments"

The roots of today's epidemiology are more clearly detectable in the work of William Farr, a physician given responsibility for medical statistics in the Office of the Registrar General for England and Wales in 1839. The Annual Reports of the Registrar

General during the subsequent 40 years established a tradition of careful application of vital data to problems of public health and to other broad public concerns. Some of the matters to receive Farr's attention included mortality in the Cornish metal mines and other occupational settings, in prisons and other institutions, and among married and single persons, fluctuations in the marriage rate as an index of the economic health of the country, the distribution of cholera, trends in the literacy rate, the value of a person in terms of money, and the consequences to England and Wales of the 19th century emigration. The thoroughness of Farr's analyses can be illustrated by his attempt to ascertain the effect of imprisonment on mortality [172]. He determined the population at risk as well as the number of deaths, compared the prison death rate with that in the general population, took into account the age of the prisoners and the duration of their stay in prison, and considered the fact that "prisoners rarely labour under any serious disease at the time of their committal." Finally, he computed what we shall later refer to as an attributable risk and concluded, "Only 8 criminals were executed (in) 1837, while . . . the average annual number of deaths due to imprisonment was 51." In considering the population at risk, the need to take into account differences in the characteristics of compared groups, the biases involved in the selection of persons exposed to a suspected cause, and ways of measuring excess risk, Farr identified some of the major concerns of epidemiologists today.

One of Farr's contemporaries was a physician most widely known for his administration of chloroform to Queen Victoria during childbirth, but remembered among epidemiologists for his demonstration of the spread of cholera by fecal contamination of drinking water. We shall refer to the work of John Snow in several contexts but, from the methodologic point of view, his most interesting investigation was the demonstration that cholera risk was related to the drinking water supplied by a particular commercial company in London and, by inference, to the source from which the company obtained its water [375].

Snow noted that in 1849 cholera rates were particularly high in areas of London supplied with water by the Lambeth Company and by the Southwark and Vauxhall Company, both of

which drew their water from the Thames River at a point heavily polluted with sewage. Subsequent to the relocation between 1849 and 1854 of the Lambeth Company's source to a less polluted area of the river, the incidence of cholera declined in the areas of the city supplied by that company. During the same time period there was no change in the incidence of the disease in areas supplied by the Southwark and Vauxhall Company which continued to draw its water from the most polluted area of the river. The situation in 1854 is illustrated in Table 1. The

Table 1

Mortality from cholera in the districts of London supplied by the Southwark and Vauxhall Company and by the Lambeth Company, July 8 to August 26, 1854*

Districts with water supplied by	Population, 1851	Deaths from cholera	Cholera death rate per 1000 population
Southwark and Vauxhall Company only	167,654	844	5.0
Lambeth Company only	19,133	18	0.9
Both companies	300,149	652	2.2

* From Snow [376].

areas of London supplied entirely by the Southwark and Vauxhall Company experienced a rate of 5.0 deaths from cholera per 1000 population, whereas the death rate in the areas supplied entirely by the Lambeth Company was only 0.9 per 1000. A large area supplied by both companies experienced 2.2 deaths per 1000, a rate midway between those for the areas supplied by either company alone.

Snow saw that these observations were consistent with the hypothesis that persons drinking water supplied by the Southwark and Vauxhall Company had greater risks of cholera than those drinking Lambeth Company water. However, he also realized that many factors other than water supply could differ between these geographic areas and parallel the observed variations in

cholera rates. Snow's genius lay in his recognition of a circumstance by which the hypothesis implicating the water supply could be put to a crucial test. In his own words [376]:

> . . . the intermixing of the water supply of the Southwark and Vauxhall Company with that of the Lambeth Company, over an extensive part of London, admitted of the subject being sifted in such a way as to yield the most incontrovertible proof on one side or the other. In the sub-districts enumerated in the above table as being supplied by both Companies, the mixing of the supply is of the most intimate kind. The pipes of each Company go down all the streets, and into nearly all the courts and alleys. A few houses are supplied by one Company and a few by the other, according to the decision of the owner or occupier at that time when the Water Companies were in active competition. In many cases a single house has a supply different from that on either side. Each company supplies both rich and poor, both large houses and small; there is no difference either in the condition or occupation of the persons receiving the water of the different Companies. Now it must be evident that, if the diminution of cholera, in the districts partly supplied with the improved water, depended on this supply, the houses receiving it would be the houses enjoying the whole benefit of the diminution of the malady, whilst the houses supplied with the water from Battersea Fields would suffer the same mortality as they would if the improved supply did not exist at all. As there is no difference whatever, either in the houses or the people receiving the supply of the two Water Companies, or in any of the physical conditions with which they are surrounded, it is obvious that no experiment could have been devised which would more thoroughly test the effect of water supply on the progress of cholera than this, which circumstances placed ready made before the observer.
>
> The experiment, too, was on the grandest scale. No fewer than three hundred thousand people of both sexes, of every age and occupation, and of every rank and station, from gentlefolks down to the very poor, were divided into two groups without their choice, and, in most cases, without their knowledge; one group being supplied with water containing the sewage of London, and, amongst it, whatever might have come from the cholera patients, the other group having water quite free from such impurity.
>
> To turn this grand experiment to account, all that was required was to learn the supply of water to each individual house where a fatal attack of cholera might occur.

Within the districts supplied by both companies, Snow inquired of relatives and others as to which company supplied

water to every house in which a death from cholera had occurred between July 8 and August 26, 1854. The results are shown in Table 2. The cholera death rates for customers of each company

Table 2

Mortality from cholera in London, July 8 to August 26, 1854, related to the water supply of individual houses in districts served by both the Southwark and Vauxhall Company and the Lambeth Company*

Water supply of individual houses	Population, 1851	Deaths from cholera	Cholera death rate per 1000 population
Southwark and Vauxhall Company	98,862	419	4.2
Lambeth Company	154,615	80	0.5

* From Snow [376].

were similar to those (seen in Table 1) of the same company's customers in the districts supplied exclusively by that company. Moreover, the death rate for customers of the Lambeth Company was no higher than that for the rest of London, even though the majority of the Lambeth Company's customers were located in the area supplied also by the Southwark and Vauxhall Company—an area in which the epidemic raged severely. The hypothesis that the drinking of water supplied by the Southwark and Vauxhall Company was associated with death from cholera was therefore supported.

Snow's utilization of this "natural experiment" focuses attention on the value of searching out unusual circumstances that can be used to test hypotheses. In his determined exploitation of the circumstance when found, Snow demonstrated the force of the arguments that can be developed from nonexperimental kinds of hypothesis testing. Sometimes, the test provided by such natural circumstances approaches the rigor of that of actual experimentation. In recent years, a series of studies remarkably comparable to those of Snow has resulted in the linking of "Blackfoot Disease" (peripheral vascular disease and gangrene)