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Chapter 1

Introduction

Since *Clinical Epidemiology* means different things to different people, the first job of a book with that title is to define itself. The word *epidemic* was originally used as a name for outbreaks of contagious disease in humans (in contrast to *epizootic* outbreaks in animals) and is derived from the Greek επι = upon and δεμος = people. *Epidemiology* is thus the study of people. More specifically, in epidemiologic studies the data refer to groups of people and the fundamental unit under observation is a person, in contrast to the animals, inanimate substances, human organs, or human fragments that are the basic materials investigated in other forms of medical research. The prefix *clinical*, which comes from the Greek κλινικος = bed, refers to sick people and to the activities conducted in the care of patients. A reasonably close etymologic definition, therefore, is that clinical epidemiology is concerned with studying groups of people to achieve the background evidence needed for clinical decisions in patient care.

With this focus of concern, clinical epidemiology contains certain important distinctions in its point of view, topics of interest, and methods of research. In point of view, clinical epidemiology represents the way in which classical epidemiology, traditionally oriented toward general strategies in the public health of community groups, has been enlarged to include clinical decisions in personal-encounter care for individual patients. In topics of interest, clinical epidemiology emphasizes issues in diagnosis, prognosis, therapy, and other distinctively clinical judgments that are usually omitted from the traditional inventory of contents in public health. In research methods, clinical epidemiology is concerned with the procedures and standards needed for scientifically rigorous studies of the complex clinical phenomena that occur in intact people. These methods are important both for the investigators who do the research and for the readers who struggle to understand and interpret the published results.

The remainder of this introductory chapter provides a historical background, describing the way in which traditional epidemiologists and traditional clinicians have migrated from their classical activities to create clinical epidemiology as a new intellectual domain in modern medical science.

1.1. THE EPIDEMIOLOGIST'S MIGRATION TO CLINICAL MEDICINE

Because epidemiology began with studies of the contagious outbreaks that were called *epidemics*, infectious diseases have been the basic source of concepts, methods, and technology in epidemiologic research. Almost all the activities of contemporary epidemiology, including its customary academic location in departments with such names as public health and preventive medicine, are derived from a heritage of infectious disease and from the pioneering role of microbiology in the evolution of medical knowledge.

In the chronology of medical science, infectious diseases were among the first human ailments that could be (1) identified during life by a specific laboratory test; (2) attributed to a demonstrable causal agent; (3) avoided by appropriate sanitation; and (4) prevented by individual treatment (with vaccination) of susceptible hosts. Infectious disease brought each of these four innovations to the study of human illness, and each innovation gave epidemiologists a focus of interest and set of research methods:

1. With bacteriologic procedures providing accurate identification of diseases, the rate of occurrence and geographic distribution of the diseases could be studied effectively.

2. The laboratory tests of bacteriology did more than identify a disease; they simultaneously demonstrated a causal agent. The ability to demonstrate causes of disease led epidemiologists to become concerned with problems of etiology not only for infections but for other diseases as well.

3. Because the community rather than the hospital was the site of study of both sanitation and the occurrence rate of disease, epidemiologists became interested in outpatient populations and in the diverse problems of public health.

4. Although sanitation helped to prevent disease in the general population of the community, vaccination provided protection to individual persons and thus advanced the conversion of epidemiology into an experimental discipline. To test new vaccines, epidemiologists had to study individual people while performing group experiments called *clinical trials* and using statistical procedures for design and analysis.

As a consequence of these different developments, epidemiology has become intellectually housed in academic sites with a wide diversity of names: hygiene, public health, preventive medicine, social medicine, community medicine, and even biostatistics. The personnel include physicians and nonphysicians with a wide variety of talents and interests. Among the nonphysicians are nurses, dentists, and veterinarians; virologists, parasitologists, and other microbiologists; geneticists, biometricians, biostatisticians, and computer experts; and people who specialize in occupational and industrial medicine, in hospital administration, and in programs of medical care. The different pursuits of these many people reflect the persistent interest of departments of epidemiology in infectious disease but also indicate a broad expansion into other clinical domains:

1. Statistical tabulations of occurrence and distribution for infectious epidemics have been extended to include rates of both mortality and morbidity, and the diseases under study, once only infectious and acute, are now also noninfectious and chronic.

2. Although causes of infectious diseases can be demonstrated by experiments in animals, the causes of chronic disease in people are not amenable to experimentation and are studied instead with statistical comparisons of data obtained from observation of naturally occurring human events.

3. Attention to community health, which previously created a challenge mainly in preventing disease with methods such as improved sanitation and nutrition, has now produced major clinical challenges in the quality, distribution, and economics of medical care.

4. The statistical procedures developed for clinical trials have been extended to include not only the prevention of acute disease in healthy persons but also the treatment as well as the prevention of chronic disease.

1.2. THE CLINICIAN'S MIGRATION TO EPIDEMIOLOGY

At the same time that classical epidemiologists have extended their boundaries from infectious disease to many other clinical territories, classical clinicians have developed many epidemiologic interests and concerns. As students of prognosis and therapy in human illness, clinicians have always been epidemiologists in the original sense of the word, but certain activities of modern clinical investigators—using statistics, studying groups of people, and delivering preventive therapy—are traditionally regarded as epidemiologic:

1. Every act of decision in diagnosis, prognosis, and therapy involves an assessment of probabilities and is thus a type of statistical exercise.

2. To make those decisions, clinicians recall their experience with previous patients, divide those patients into collections of subgroups or series, and compare the present patient with those in the various collections. These clinical subgroups and series correspond to what epidemiologists often call cohorts and populations.

3. In following the long-term outcome of treatment in chronic diseases, a clinician must leave the inpatients observed in the wards and pavilions of the hospital and must study outpatients in clinics and in community settings—the traditional locale of the epidemiologist.

4. Although clinicians do not usually regard treatment as an act of *preventive* medicine, many drugs and operations used in contemporary therapy are prophylactic rather than remedial. Their purpose is not so much to change an existing abnormality as to keep an already diseased patient from getting worse. For example, antithrombotic therapy is used not to remedy the lesion of a myocardial infarction but to prevent thromboembolic phenomena or recurrent infarction. In these prophylactic types of treatment, the goal is to prevent a more serious clinical state that does not yet exist. With this type of therapy, the clinician engages in preventive medicine—the epidemiologist's traditional concern.

1.3. THE CONTENTS OF CLINICAL EPIDEMIOLOGY

These two kinds of intellectual migration have brought many epidemiologists and clinicians into a common territory in which both groups operate, independently or in collaboration, with mutual interests and mutual techniques. As a new domain among the various divisions of contemporary medicine, clinical epidemiology is characterized neither by disease in a particular organ system (such as cardiology and endocrinology), nor by the age of the diseased subjects (such as pediatrics and geriatrics), nor by data derived from a particular form of technology (such as biochemistry and microbiology). In clinical epidemiology, any type of disease can be studied: acute or chronic, anatomically localized or diffuse, infectious or noninfectious. The subjects can be of any age: newborn or senile, young or old; and the data can be contributed by any useful technology of laboratory or bedside, ranging from electron microscopy to naked eye and from digital computer to perceptive human mind.

The distinguishing characteristics of clinical epidemiology are in its foci of investigation, its material, and its methods. The foci of investigation are topics in the occurrence, distribution, causation, diagnosis, natural history, prognosis, prevention, and therapy of disease. The unit of material in the investigation is a person rather than an animal, tissue, cell, or molecule. In some of the studies, the person will have been exposed to an agent

suspected of causing a disease, and in many other studies, the person will be a patient who was treated with an agent intended to prevent or to alter a disease. The methods of investigation include techniques for identifying the characteristics of individual human hosts, for appropriately classifying those hosts and dividing them into groups, for comparing the results obtained in different groups, and for analyzing the importance of any observed differences.

The distinction between clinical and classical public health epidemiology can often be discerned by answering the question, What's in the denominator? For the various means, rates, and proportions that are examined in classical public health epidemiology, the denominator usually contains a *general population*, determined by the census counts (or sometimes by special surveys) of a particular geographic region, such as a city or nation. In clinical epidemiology, the denominator usually contains a *clinical group*, determined by studies of people with a particular clinical condition or disease.

This new definition of *clinical epidemiology* gives it a wider range of activities than those contained in previous applications of the term. When John R. Paul (in 1938 and later in 1958)[1,2] (Fig. 1–1) originally added the word clinical to epidemiology, his goal was to extend epidemiology beyond statistical rates of disease and beyond infectious ailments alone to encompass "the circumstances under which diseases occur, where diseases tend to flourish, and where they do not." This approach—which includes environmental, occupational, cultural, and other community aspects of disease as well as the traditional studies of contagion—has sometimes been called *ecologic medicine*, *social medicine*, or *community medicine*. Although an obvious part of the collateral concerns of clinical epidemiology, these ecologic territories have now become generally recognized as part of the intellectual domain already under epidemiologic surveillance.

The newer usage of clinical epidemiology is intended to join the particular skills and

Figure 1–1. John R. Paul (1893–1971). (Courtesy of Dr. Dorothy Horstmann.)

knowledge that distinguish both the clinician and the epidemiologist. In clinical epidemiology, "clinical" preserves its connotations of human illness, and "epidemiology" preserves its connotation of groups of people. The addition of clinical sophistication to epidemiology can improve the medical interpretation of data used in studying occurrence rates and causes of disease; and the addition of epidemiologic methods to clinical medicine can help clinicians in their problems of evaluating different modes of treatment for patients. The particularly new things for the conventional epidemiologist in clinical epidemiology are the topics of clinical course and therapy for disease; the new things for the conventional clinician are the statistical organization and analysis of data from human groups.

Clinical epidemiology gets its intellectual heritage and its founding fathers from both of the "families" that it unites. The clinical heritage dates back to Hippocrates and to Thomas Sydenham, whose concern with human sickness always included an appreciation of human environment; the populational heritage dates back to John Graunt, who instigated, and to William Farr, who developed, procedures for tabulating disease rates in what is now often called *vital statistics*. Among the principal early explorers of the clinical epidemiologic domain were Pierre Ch. A. Louis (Fig. 1–2), who introduced the numerical method for investigating results of treatment; Ignaz Semmelweis (Fig. 1–3), who analyzed the results of inpatient therapy to demonstrate the iatrogenic etiology of puerperal fever; and Austin Bradford Hill (Fig. 1–4), who helped develop and popularize statistically rigorous clinical trials.

The domain of clinical epidemiology is now the site of increasingly active exploration. Within the past few decades, major advances in diagnostic tests have been followed by many studies designed to appraise old data or to obtain new data on the distribution and

Figure 1–2. Pierre Ch. A. Louis (1787–1872). (Courtesy of Yale Medical Historical Library.)

Figure 1-3. Ignaz Semmelweis (1818–1865). (Courtesy of Yale Medical Historical Library.)

clinical course of disease. Many new investigations of human populations have resulted from the search for cause in such chronic illnesses as cancer and arteriosclerosis. The causative clues obtained from these and other investigations have been followed by large-scale clinical trials, checking whether the diseases can be prevented by changes in nutrition, environment, or life style. The expansion of diagnostic technology has led to many problems in deployment of intricate machinery and evaluation of the costs and benefits of the tests. Also, the spectacular new modes of surgical and pharmaceutical therapy have produced a steady proliferation of statistical investigations of the new treatments. Even if no other reasons existed, the importance and increasing frequency of these investigations would require the delineation of clinical epidemiology as a medical domain that can provide an intellectual home for the activities.

1.4. THE METHODS OF CLINICAL EPIDEMIOLOGY

The topics that have just been described form the contents of the conjoint domain in which the classical epidemiologist—oriented in statistics, populations, and preventive medicine—meets the classical clinician—oriented in the artful science of diagnosis, prognosis, and care of individual patients.

Clinical epidemiology, however, can also be defined methodologically as a domain that is concerned with research involving intact human beings. The methods used in such research are necessarily different from the customary procedures used in other scientific domains. In traditional scientific concepts and teaching, research consists of experiments performed in laboratories. In a laboratory setting, the investigator can choose the animals

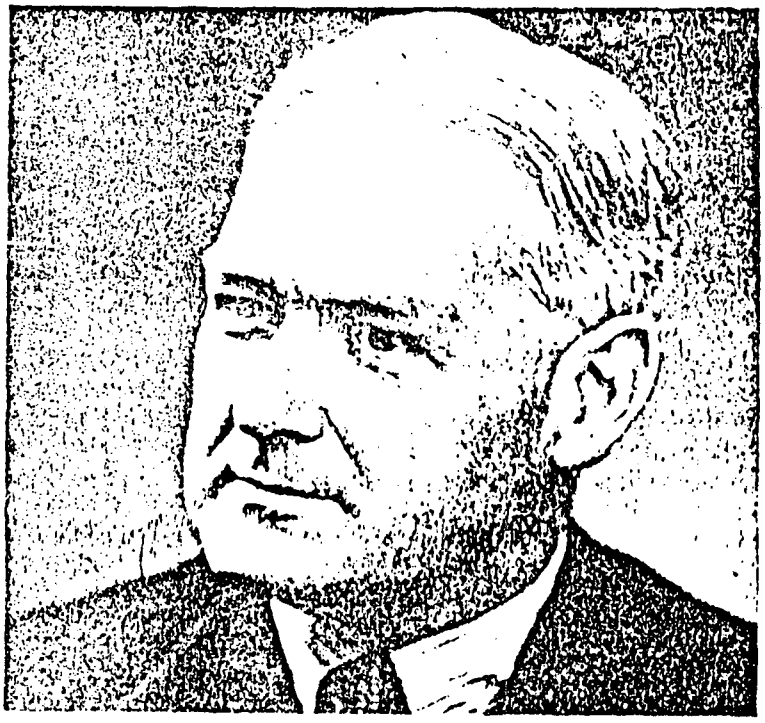

Figure 1–4. Austin Bradford Hill (1897–). (Courtesy of Editors, Statistics in Medicine.)

or inanimate substances that are the materials to be studied, divide them to form groups in any desired manner, subject them to whatever procedures have been chosen as the interventions, obtain accurate data with diverse technologic devices, and even kill (or "sacrifice") the material to verify the data and to see precisely what has happened.

These options are seldom available in research on intact human beings. Most of the data that are studied to make decisions about the etiology, distribution, diagnosis, prognosis, and therapy of human ailments come from ordinary observations, not from experiments, of events occurring during the routine activities of daily living for the people under scrutiny. The investigator does not decide who will smoke or not smoke, exercise or not exercise, breast-feed or not breast-feed. Except in the extraordinary experiments of randomized clinical trials, the investigator also does not decide who will be treated with medication, surgery, or watchful waiting, and does not choose the type of medication or surgery. All these decisions are usually made, without concern for experimental protocols, by the people under investigation and by their clinical advisors. The data used in the investigations can often come from technologic measurements [illegible] and other substances, but

Because a laboratory investigator can usually conduct experiments, form groups, assign interventions, and rely on technologic information, the research can easily satisfy the fundamental scientific requirements for fair comparisons and trustworthy data. The investigator's main creative challenges, therefore, often occur in the formulation of ideas to be explored. The investigator must use imagination, verve, and insight to choose both the

hypotheses that will be studied and the appropriate counterhypotheses that must be ruled out.

In research with individual persons or groups of people, however, the investigator can seldom perform experiments; the groups are usually self-selected or assigned without experimental planning; and the data are often obtained from human recollections and judgments. In these circumstances, the fundamental requirements of science are seldom easy to fulfill, and the investigator becomes creatively challenged, at a more basic scientific level, by problems in methodology itself. In the midst of information that is not acquired with the rigor of experimental planning in the laboratory, how can the investigator arrange to obtain trustworthy data and fair comparisons? How can statistical tabulations of observational information be obtained and analyzed in a manner that encourages confident belief in the results and credible acceptance? Even when an experimental clinical trial can be arranged with a group of people, the experimental plans and interpretations are inhibited by many human or clinical constraints that are not pertinent to laboratory research and that need not limit the creativity of the laboratory investigator. In the midst of these inhibitions, how can clinical investigators conduct experiments that satisfy the standards of science while answering the questions asked in clinical practice?

These scientific challenges in the performance and evaluation of human research are the main methodologic concerns of clinical epidemiology, and they will be the prime topics for subsequent discussion here.

1.5. SYNOPSIS

We can summarize the foregoing discussion by noting that clinical epidemiology is a domain of both content and methods. In content, clinical epidemiology is concerned with the etiology, diagnosis, prognosis, and care of human illnesses. The concept of *care* encompasses the strategy of therapy as well as the arrangements used to deliver therapy, and the concept of *therapy* refers to remedial or prophylactic treatment of individual patients. The methods of clinical epidemiology are intended to bring clinical sophistication and scientific rigor to the difficult challenges of investigating phenomena that occur in free-living intact people, who often cannot be studied with experimental plans.

1.6. A NOTE ABOUT THE EXERCISES

Each chapter in this book is followed by a set of exercises that can be used in any way that readers or instructors wish. The exercises were developed, and have been used for the past few years, as part of a special seminar conducted for postgraduate physicians. In that course, the written text for each chapter was read by the individual participants without any didactic lectures. The exercises provided additional illustrations and problems to challenge the reader's understanding of the subject. The written solutions to these exercises, which were turned in for review and annotation by the instructor before each class, then formed the main focus of discussion in the classroom seminars.

Suitable exercises for this type of material are not easy to create. Although many (in fact, most) of the assignments are based on events that have actually occurred in clinical or epidemiologic research, too much time would be consumed if the reader had to review a complete published report to find the particular items selected for discussion. Consequently, to allow prompt focus on the selected topic, the exercises are presented mainly as excerpts or brief summaries of the published reports. Specific references are seldom cited for these reports, because many of the exercises were chosen to depict undesirable procedures and because many other errant publications could have been selected instead.

In many ways, the exercises are the best part of the book. Medical students and practicing clinicians constantly complain about the enormous amount of memorization and the minuscule amount of thinking that is contained in medical education. These exercises are intended to make you think. Because they deliberately make use of the reader's clinical knowledge, they should give medically oriented persons the intellectual "fun" of relying on what they already know as a basis for solving problems and as a background for learning new things. The goal is to stimulate your thoughts not merely about the preceding text and the specific assignment presented in each exercise, but particularly about the challenges that regularly confront you when you read the medical literature, attend meetings where research is presented, or even do research yourself. In many instances, an exercise will reveal something you did not perceive in the text, force you to reevaluate your understanding of a particular subject, or let you see how your clinical knowledge, rather than the unfamiliar tactics of epidemiologic methods, provides the crux of the answer to many questions.

The publishers have persuaded me that answers to the exercises should be contained in the back of the book rather than issued as a separate document. Although it may be tempting, I urge you not to look at the answers until you have first thought each one through and preferably written down your solution. If this were a text on statistics, seeing the answers in advance would not quench your thought process, because you would still have the challenge of deciding what formula to use and showing that you can work your way through the calculations. Most of the exercises in this book, however, depend mainly on what you think and how you think about it. If you look at the answers prematurely, their revelation will make you miss the stimulation, the learning, and the fun.

Unlike the numerical answers that are unequivocally right or wrong for the customary exercises in a book on statistics, the answers to many of the exercises here are matters of judgment. To give the reader an idea of how someone else might answer the questions, a set of "official" answers has been prepared for each exercise. These answers, however, are merely official. They may be right or wrong, according to the judgment of the reader or the instructor. Because the goal of the exercises is to aid understanding and provide stimulation, the discussion provoked by debate about the correctness of an answer may sometimes be much more enlightening than the content or merit of the answer itself.

1.7. A NOTE ABOUT REFERENCES

To avoid repetitious listings and to save space while maintaining convenience for the reader, the bibliographic references in the text are identified in two different ways. The references are noted with sequential numbers as they appear successively within each chapter. At the end of the chapter, the numbers indicate the name of the first author and year of publication for that reference. The name of the journal is added, and sometimes letters (such as a, b, c) are appended, when needed to distinguish several references by the same author in the same year.

This end-of-chapter information will guide you to the full citation of the reference, which is listed separately at the end of the book, starting on page 738. In that section, each reference is completely identified and arranged alphabetically according to the first author. At the end of each alphabetized reference, the numbers in brackets indicate the chapter(s) in which that reference is mentioned.

EXERCISES

Exercise 1.1. In retrospective case-control studies of the etiology of a particular disease, the denominators for the compared results are obtained from a *case* group

consisting of people who already have the disease and a *control* group consisting of people who do not have the disease. The members of the case group are usually chosen from patients seen at a hospital or other medical setting. The members of the control group may be chosen from patients who have other diseases or from healthy people in the community. Information about previous exposure to the suspected etiologic agent is then obtained from each member of both groups, and the rates of previous exposure are compared.

In Section 1.3 of the text, the contents of the denominator were said to provide the distinction between clinical and classic public health epidemiology. Using that distinction, which of these two domains is the proprietor of retrospective case control studies?

Exercise 1.2. Epidemiologists today engage in four types of activities that have received relatively little discussion in Chapter 1. Do you think these activities, which are described here, are part of classical or clinical epidemiology?

1.2.1. Clinics established at medical centers to give special attention to patients with occupation-associated diseases.

1.2.2. Seroepidemiologic surveys of children in different communities to analyze the results of antibodies for diverse infectious diseases.

1.2.3. Nosocomial epidemiologic studies to determine the transmission of infection to and among hospitalized patients.

1.2.4. "Detective-work" epidemiologic activities to determine the causes of such relatively new clinical illnesses as Legionnaire's disease, toxic shock syndrome, or AIDS (acquired immune deficiency syndrome).

CHAPTER REFERENCES

1. Paul, 1938; 2. Paul, 1958.