Epidemiologic Methods and Methodologic Vigilance

IN ASSESSING the association between suspected risk agents and diseases, clinical readers must frequently evaluate evidence from epidemiologic studies whose designs differ considerably from the "ideal" scientific methods of experimental research such as the randomized clinical trial. The difficulties in carrying out these observational epidemiologic studies often result in the use of research procedures that do not adhere to the usual requirements for validity inherent in the paradigm of the experimental clinical trial. These violations in the research designs of individual studies may lead to criticisms that are based on speculation about "possible" sources of bias, even though there may be no empirical evidence to support the speculations. In this issue of the *Journal*, two papers provide empirical evidence for the existence of a previously-hypothesized bias. Our editorial comments are intended to help the reader understand the source of the bias and its importance. But before considering the problems of bias in observational studies, we need first to consider why they are used as substitutes for experimental trials.

The randomized trial is now widely accepted as the scientific standard for evaluating cause–effect relationships in medicine. Unfortunately, despite their obvious scientific advantages, experimental trials can rarely be used to investigate causal relations in epidemiologic research. Ethical and logistic barriers to performing experiments have forced epidemiologists to rely instead on observational studies in which people receive the suspected risk factor not by randomization but by personal choice (e.g., cigarette smoking), by imposition (e.g., as a prescribed medication), or by innate processes (e.g., elevated cholesterol or blood pressure).

In choosing a non-experimental observational study design, the investigator can select either a cohort design or a cross-sectional design (such as a retrospective case–control study). The observational cohort study, which most closely resembles an experiment, has the same basic structure and "forward direction" as an experimental trial, but the suspected risk agents are not assigned by randomization.

Unlike in the cohort study, in which the investigator observes the development of the outcome, in cross-sectional research the outcome has already happened before the groups under investigation are assembled. What is left for examination in cross-sectional studies is part of an "original"—but not identifiable—cohort. The results in a cross-sectional study can rarely be an accurate representation of what happened in this original cohort. For example, a cohort can, over time, either gain or lose members between its inception and the time it is sampled by the investigator. Some of the original members of the cohort may have "migrated out" because of death or because of having left the area under observation, while others may have "migrated in." Importantly, both cross-sectional studies and cohort studies that exclude members present at inception may not contain the data that allow investigators to describe the composition of the "original" inception cohort or how it may have changed.

Two papers in this issue of the *Journal* address specific components of these problems of migration. The theoretical basis of in-migration was proposed by Joseph Berkson in 1946.[1] Berkson theorized that if patients with different diseases are hospitalized at different rates, distortions may arise when data from a hospital population are used to draw conclusions about the joint occurrence of diseases and risk agents. For nearly 30 years the problem Berkson proposed remained undocumented, until a group of scientists directly assessed the concurrence of diseases and exposures in a community population and in the corresponding hospital population.[2]

The theoretical basis of out-migration bias was suggested in 1954 in an essay by Jerzy Neyman.[3] In cross-sectional studies, or in cohort studies that examine at a later date those who were exposed earlier as part of an inception cohort, the relative proportions of the agent–outcome relationships may be seriously distorted. For example, suppose that an agent kills a substantial proportion of people soon after they receive it. A cohort consisting of people who have been receiving the agent for a number of years will systematically exclude all of the people who died early, and the remaining cohort will have a misleadingly long survival. This bias can occur in diverse ways other than by the early death of some patients, including out-migration of some living cohort members, by the investigator's decisions in collecting data, or by decisions made when living cohort members accept or decline invitations to participate in the reserach.

The bias that Neyman proposed should not be viewed as the idle speculation of an ivory-tower academic. His suggestion was provocative and constituted a major challenge to the scientific integrity of observational epidemiologic methods. Neyman's bias has been used to explain the discrepant results of diverse clinical studies, including the attempt to reconcile the contradictory reports evaluating the relationship between postmenopausal estrogen therapy and cardiovascular disease.[4,5] For that reason, we welcome the publication in this issue of the *Journal* of the two articles that provide empirical

support for Neyman's theoretical proposal.[6,7] Each helps to define a particular part of the spectrum of this bias in the assembly and maintenance of study groups. What the papers are unable to achieve is a convincing demonstration that the quantitative effects of the bias are substantial. Further studies that encompasss a broad range of agent–disease relationships are needed to estimate the quantitative importance of the bias.

Despite this limitation, these two studies of Neyman's bias contribute to a growing tradition of methodologic vigilance that helps to enhance the scientific quality of observational epidemiologic research. Observational epidemiologic studies have become increasingly important because they offer an alternative to the unfortunately often-unattainable "gold standard" of the randomized clinical trial. Acceptance of observational studies cannot occur, however, until they are perceived to have achieved the standards and rigor of research in other scientific disciplines. —*Ralph I. Horwitz, MD, and David F. Ransohoff, MD, Departments of Medicine and Epidemiology, Yale University School of Medicine, New Haven, CT 06510*

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From Clinical Epidemiology to Clinical Economics

SOMETHING INTERESTING seems to be happening to pharmaceutical advertisements in medical journals. Ads that used to tout superior safety or efficacy are now also advertising how much more economical the drug is. Advertising copywriters seem to think that physicians will consider cost in their clinical decisions. Health care administrators certainly hope that they will.

The increasing attention to cost in medical decision making reflects a broader change in medical thinking, one that places the doctor–patient relationship in the larger context of populations and social considerations. This relationship has been the major emphasis of clinical epidemiology.

The fiftieth anniversary of clinical epidemiology is May 2 this year. It has been a half century since John R. Paul gave the President's Address to the American Society for Clinical Investigation in Atlantic City and called for a new science, to be called clinical epidemiology.[1] The practitioner of clinical epidemiology, he urged, would "place his patient in the pattern in which he belongs, rather than to regard him as a lone sick man who has suddenly popped out of a healthy setting." Clinical epidemiology has made its mark, particularly during the past two decades, by adopting methods of inquiry previously applied to questions of public health, and by demonstrating their potential for solving questions of clinical practice and medical decision making. Textbooks have codified the new discipline, and its techniques are being exported to clinicians in developing countries with the support of benefactors such as the Rockefeller Foundation and the Agency for International Development.

In the same way that clinical epidemiology has bridged the care of individuals with the health of populations, there is emerging a parallel approach to placing clinical decisions in a larger context—using economic analysis to assess clinical strategies. This sister discipline, which can be called clinical economics, is being practiced by physicians and other analysts who are interested in how well resources are used. Clinical economics enables the evaluation of efficiency to join studies of efficacy and effectiveness in assessing medical practice.

Fifty years ago John Paul might have hoped that pharmaceutical companies would support their claims of effectiveness with randomized trials and their assertions of safety with case control studies. It is less likely that he would have anticipated today's attention to cost effectiveness. But today's concern about cost is not new. It is rooted in a fundamental principle of economics—that there are, and always will be, too few resources to satisfy all our desires. What is newer is the rigorous application of economic methods to clinical questions. Economics is the study of choice among alternative uses of scarce resources, and it can guide choices among alternative clinical strategies, in each case trading resources for clinical gains.

Clinical economics bridges clinical medicine and economics and forms a subset of health eco-