

Foreword

We all face disease as part of life, but the sadness it brings is all the more poignant when the disease results from drugs intended to promote health rather than to impair it. Drugs are developed and used to prevent or mitigate disease and pain, and our continued reliance on them is a testament to their wondrous efficacy and safety. But agents that have the power to alter some biological processes to our benefit can alter other biological processes to our detriment, sometimes in occult and surprising ways. To live up to the dictum that we should first of all do no harm, or at least less harm than good, we must bring our best evaluative alternative methods to bear on the measurement of drug effects, both beneficial and adverse.

Pharmacoepidemiology is a natural crossing of scientific paths. Epidemiology is the study of disease occurrence, and pharmacology aims to reduce disease incidence and prevalence through biochemical intervention. The heavy reliance on epidemiologic methods — I include among these the clinical trial — in modern drug development has been instrumental in producing a pharmacopoeia of highly effective and reliable medicines that are among the major contributors to a better quality of life. Epidemiologic methods also have provided crucial insights into modern iatrogenic epidemics, such as adenocarcinoma of the vagina caused by diethylstilbestrol, endometrial cancer caused by exogenous estrogens, and toxic shock caused by the use of tampons.

The escalating health consciousness of our society guarantees an even broader role in the future for pharmacoepidemiologic research. Drug trials for efficacy usually have been clinical trials, aimed at improving the prognosis or symptoms of patients with active disease. Field trials, which evaluate the efficacy of primary preventives, are much more ambitious undertakings. They ordinarily require many thousands of subjects to be followed for long periods, presenting difficult logistical problems. Because these subjects are not ill, recruiting them and maintaining contact is more of a problem than in clinical trials, in which the clinic can be used for both recruitment and follow-up. For these reasons field trials of pharmaceutical agents for primary prevention have been conducted only rarely, usually for vaccines. With growing interest in the primary prevention of disease, however, field trials of disease preventives may become more common.

We shall also see more studies that evaluate adverse drug effects, many of which will be case-control studies. Unintended drug effects (UDEs) that occur soon after the administration of a drug are usually discovered early in clinical testing, provided that they occur frequently enough. When UDEs are rare or occur only with a lengthy induction time, however, they may easily go undetected. Case-control studies provide an opportunity to investigate rare or delayed

UDEs without undertaking cumbersome follow-up studies of awesome cost and logistical complexity. One big obstacle to case-control studies of drug use has been ascertaining the drug history. Information about drug use recorded in medical records varies in quality and completeness, often being little better or even worse than the information about drug use stored in the cerebral cortex of users. Obtaining valid information on drug use is aided greatly by systems that automatically record drug information in computer-readable form as it is prescribed or dispensed. (Of course, even this information differs from actual use.) Automated databases that include drug information and the capability to link it with medical records are increasing in number, and with passing time accumulating data become more valuable as resources for pharmacoepidemiologic research.

Even with the best data resources, there remains a crucial epidemiologic problem in the study of many UDEs: confounding stemming from the indication for drug use. The causal association between illness and drugs employed to treat the illness can make it difficult or impossible to distinguish whether it is the drug or its therapeutic indication that is responsible for subsequent disease occurrence. Even when people with the same disease are treated with different therapies, there are usually important biologic differences among these groups. Confounding from other drugs and the possibility of drug interactions further complicate research of this type. Except in randomized trials, these problems will challenge pharmacoepidemiologists to the limits of their ingenuity and knowledge, making pharmacoepidemiology a proving ground for advances in epidemiologic methods.

Nevertheless, the basic tools to deal with these problems exist, and will inevitably become more refined as researchers gain experience, but the application of currently accepted epidemiologic principles could improve the understanding of many drug effects. For example, a disease such as "analgesic nephropathy" might cease to exist under the scrutiny of epidemiologic principles. This disease is defined as kidney disease following analgesic use. Because the definition includes the presence of the hypothesized cause, it is impossible to determine whether analgesic use is associated with kidney disease, much less whether a causal relation exists that would merit the term analgesic nephropathy. Even if an association were shown to exist using a proper disease definition that was independent of exposure, confounding by the indication for the analgesic use might account for it. To address such questions requires an epidemiologic perspective. This book will help introduce this perspective to all researchers concerned with the evaluation of drug effects.

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The materials we have elected to include derive from that early course outline but were, in fact, solicited as a nine-part series in the journal *Drug Intelligence and Clinical Pharmacy*. Those materials were solicited to follow in a logical sequence that now works as this textbook. Still, no journal series, however complete, can cover the entire length and breadth of a field, much less its depth. Therefore, this book includes significant new material.

This new material includes a chapter on risk assessment providing an international perspective, and an extensive glossary on terms used in the field. The new chapter addresses the international dimensions in pharmacoepidemiology that relate to risk assessment. Further, we determined that, as in any specialized field, the field of pharmacoepidemiology had developed both a jargon and a lore of its own. This language was often needlessly confusing to the neophyte, even to the extent of discouraging excellent scientists with specialty in one, but not the other, of the disciplines that form the basis of pharmacoepidemiology from undertaking work for which they are well qualified. Therefore, we have appended the requisite glossary.

Perhaps it goes without saying (except in a preface like this) that the real reason for this endeavor is the conviction of the three of us that the activities of pharmacoepidemiology are important. It is important for therapeutics, for medicine, for public health, and, hopefully, for the public's health. It is probably necessary to underscore that verity here, because there will be readers or their superiors who date back to the era before the watershed report of the Melmon Commission in January 1980 and remember a time when the contributions of the field were less respected because they were less respectable. Long-term follow-up of large numbers of people is neither easy or cheap; controlling the multiple biases of observational methodology, without knowing the tricks of the trade of the experimentalist, is likewise no easy task. Also, performing the sleuthing tasks of the epidemiologist in an arena dominated by clinicians — nurses, pharmacists, and physicians — is not always either understood or appreciated! Further, some of our predecessors have used manipulative approaches and unobtrusive methods motivated by a desire to co-opt collaborators in the quest for promotion or to distort data in the search for a good image for a drug product. Nor would we assert that the field was wholly purged itself of technical problems, attitudinal barriers, or ethical dilemmas. Most importantly, we suspect that while the potential contributions of epidemiology to pharmacology, and vice versa, are reasonably well established, a proper scientific evaluation of the actual contributions and accomplishments has been only partially undertaken. The valuable trends in the field are presented throughout the book. Chapters 7, 8, and 10 describe the emergence of affordable and powerful technologies using automated data sets. Chapters 1, 14, and 16 describe the development of meaningful products to improve medical practice and public policy and, in the process, protect people who are taking medications.

Finally, we have many people to thank for bringing this book into reality. Each of the contributors will be known by his or her works, but we would like to thank them for the energy and enthusiasm which they brought to these labors. We also

thank Barbara Hulka, and the students of "Methods and Issues in Pharmacoepidemiology" for their valuable comments. Most especially, we thank Burroughs Wellcome Co. and the University of North Carolina, whose generosity of spirit provided encouragement to undertake this task and the setting in which this endeavor can grow. Finally, we thank friends and families for understanding the importance of this effort and supporting our preoccupation with it.

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