Molecular Tools and Infectious Disease Epidemiology

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PREFACE

WHY A TEXTBOOK ON MOLECULAR EPIDEMIOLOGY OF INFECTIOUS DISEASE?

As a Professor of Epidemiology in the Hospital and Molecular Epidemiology masters' program at the University of Michigan, I frequently meet with potential students. Because our program includes laboratory training, many of these students have undergraduate degrees in biology or microbiology, and extensive laboratory experience. Why are they considering a degree in epidemiology? The most common answer is that although they enjoy lab work, they want to be in a position to see how their work at the bench "makes a difference." Making a difference in human health is a core value of epidemiology, the science that uses field, laboratory, and statistical methods to describe the distribution of health and disease in populations and the determinants of that distribution.

Molecular epidemiology combines the methodologies of molecular biology, microbiology, and other laboratory sciences with population approaches used by epidemiologists and the epidemiologic value of making a difference. Basic science research generally has an outcome of understanding the underlying mechanisms leading to a specific function. By contrast, epidemiology is very pragmatic; epidemiologists identify problems and try to fix them, and then check if the fix worked. This pragmatism goes hand and glove with empiricism: if something works, why it works is of less interest than applying it to fix the problem at hand. While this pragmatic approach can be wildly successful, there can be unintended consequences from an empirical approach. Unintended consequences frequently arise from the indirect effects of an intervention. Understanding the underlying mechanisms helps identify indirect effects. When we understand both direct and indirect effects of an intervention, we can more accurately predict when and how to apply it. Thus the merger of molecular biology with epidemiology is potentially even more powerful than the simple combination of laboratory tools with epidemiologic approaches might suggest, because molecular tools enable the epidemiologist to explore the underlying mechanisms leading to a problem of interest, and to use that understanding to better address the problem of interest.

Although the potential is great, fully integrating molecular biology with epidemiology is not easy. Interdisciplinary projects are challenging. To be successful, collaborators must learn each other's jargon and respect the strengths and be cognizant of the weaknesses of each other's disciplines. There can be arrogance on both sides; someone who has never worked in a laboratory may not appreciate the tremendous time, effort, and scientific acumen required to test out a new piece of equipment. Similarly, someone who has never conducted an epidemiologic study, nor managed, integrated, and analyzed vast amounts of data measured using different instruments that vary in quality may believe it is all common sense. On the flip side, an epidemiologist may assume that what comes from the laboratory is correct, and a laboratorian might think the same of something that comes from the computer.

THE PURPOSE OF THIS BOOK

The purpose of this book is to explore the synergies that emerge from using molecular tools in epidemiologic studies and epidemiologic approaches in molecular studies, and the challenges of conducting a study that integrates the two. My intention is to give the reader

an understanding of the challenges of designing, conducting, and analyzing molecular epidemiologic studies. The book covers enough molecular biology for an epidemiologist to read the literature and enough epidemiology to do the same for a microbiologist or molecular biologist. The substance of the text is on how to marry molecular biology with epidemiology.

Molecular biology is currently a rapidly evolving field; technological development is continuing at a ferocious pace. Any text that reviews these technologies will be out of date by the time publication is achieved. However, most of these technologies represent iterative rather than paradigm shifting changes. They are better, faster, or more efficient ways to do what can already be done. These tools make it possible to consider testing large number of individuals – which is required for epidemiology. It also makes it possible to limit the exposition in this book to the core techniques used in molecular biology and focus on the more difficult discussions that must occur for molecular epidemiology to succeed, regardless of what technologies are available. That is, how to identify the correct technique to address your research question, how the available technology frames what research questions might be asked, and how an epidemiologic study is conducted.

Though molecular epidemiology is often envisioned as measuring biological parameters in population studies using molecular tools, population approaches are increasingly incorporated into microbiology and molecular biology. Modern molecular tools have revealed that microbes are populations, and the individuals within those populations vary in ways that influence the ability to be transmitted, persist, acquire genetic changes, and cause disease. To address these questions requires epidemiology.

WHO THIS BOOK IS FOR

This book was developed for teaching the integration of epidemiology with molecular biology to senior undergraduates or masters' students. I assume students have some knowledge of basic biology, and have been introduced to thinking in terms of populations.

HOW TO USE THIS BOOK

To truly learn molecular epidemiology, it is optimal to have a training program that includes working in the laboratory, as well as on the design, conduct, and analysis of an epidemiologic study that integrates molecular tools. These experiences cannot be encompassed within the covers of a textbook. What a textbook can do is to provide a context for understanding and interpreting what is read in the scientific literature and a foundation for subsequent practical experience in the laboratory and in the field. The first three chapters give the context, summarizing the history of incorporating laboratory methods in epidemiologic studies, and presenting examples of how molecular tools are applied in epidemiology. As I assume that students using the book may come from a variety of backgrounds, Chapter 4 is a primer on epidemiology and Chapter 5 a primer on molecular biology. These chapters can be safely skipped by students that have already covered them elsewhere. Chapters 6 and 7 present molecular tools and how to choose an appropriate tool for the research question. Chapters 8 through 10 discuss how integrating molecular tools in epidemiologic studies affects the design and conduct of epidemiologic studies. Chapter 11 presents some general analytical strategies. The focus is on the challenges of integrating data across scales, from the molecular to the population. Chapter 12 considers the ethical concerns that arise in molecular epidemiologic studies. In the final chapter, some future opportunities are discussed. Although the chapters build on each other, the instructor may find reading chapters in a different order better suits their target audience. The chapters are sufficiently stand-alone that this is practical.

Depending on the students, the instructor may wish to supplement the text with a variety of other experiences. Available on the World Wide Web are numerous videos that show laboratory techniques. I ask students to find them and present them in class; this is always an enjoyable exercise. For excellent educational resources on genetics, genomics, and other omics, I suggest the learn genetics website (http://learn.genetics.utah.edu/), genomics education website (http://www.genomicseducation.ca/), and the science primer on the National Center for Biotechnology Information website (http://www.ncbi.nlm.nih.gov/About/primer/). For my own course directed at masters' students, the course revolves around designing a molecular epidemiologic study. In a series of homeworks, students explore the literature on the epidemiology of a condition, the molecular tools available to measure the outcome or exposures, and the associated ethical issues. The final paper is a grant proposal.

ACKNOWLEDGMENTS

Writing a textbook is an act of hubris. My decision to attempt it was based on my frustration in finding appropriate materials to teach a course on the molecular epidemiology of infectious diseases that addressed the issues covered here, the interface between molecular biology and epidemiology, rather than a discussion of techniques or applications. The text is based on lectures developed and discussions arising from teaching molecular epidemiology to masters' students in the Hospital and Molecular Epidemiology program in the Department of Epidemiology at the University of Michigan. I first developed this course in 1997 and have taught it almost every year since then. Therefore, I would like to thank the many students who took my course and helped me clarify my thinking about the field. I also would like to thank Carl Marrs, Associate Professor of Epidemiology at Michigan and my laboratory mentor and collaborator over the past 20 years, who made my transformation into a molecular epidemiologist possible. Lixin Zhang, an Assistant Research Professor of Epidemiology, was the first student Carl and I trained jointly in molecular epidemiology and now is a wonderful collaborator; what I have learned from Dr. Zhang about laboratory techniques during his training and since has far exceeded the reverse. I have had many other outstanding students working with me over the years, too numerous to list here, who have also helped me solidify my thinking. Thank you. I would also like to acknowledge my former Department Chair, Hunein F. Maassab, inventor of the FluMist vaccine, who kindly gave an assistant professor the physical and intellectual space required to become a molecular epidemiologist.

Each chapter of this text was reviewed by one or more anonymous reviewers. Their comments were invaluable and I truly appreciate their time and effort. I also very much appreciate the editorial staff at Elsevier who arranged for reviews and editorial assistance. The book is much better for it. Thanks also to my research staff, Usha Srinivasan and Dawn Reed, who put up with me during the writing of this text, and Anna Weaverdyck for providing the outstanding secretarial support that brought the text to closure.

Writing a book takes emotional as well as intellectual support. I am extremely grateful to my husband, Mike Boehnke, for his love and unwavering faith in my abilities to bring this book to completion.