dents, postdoctoral fellows, and colleagues and also as a practical guide to the performance and interpretation of breeding studies. I think he has succeeded perfectly.

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Genetic Variation and Human Disease: Principles and Evolutionary Approaches. By Kenneth M. Weiss. Vol. 11 in: *Studies in Biological Anthropology*. Edited by G. W. Lasker, C. G. N. Mascie-Taylor, D. F. Roberts, and R. A. Foley. New York: Cambridge University Press, 1993. Pp. 300. $69.95 (cloth); $24.95 (paper).

Finally, a realistic perspective on complex disease–predisposing genes. Through detailed analysis of the evolutionary forces that shape the entire human genetic landscape, Dr. Weiss explains why "the inevitable rush of enthusiasm to screen samples, families, or populations for causal alleles for every type of trait will produce many irreproducible results and excessive claims" (p. 306). He goes on to conjecture that "we will be forced to accept that we cannot understand a trait well by enumerating all of its individual 'causes,' which will be quixotically ephemeral and environmentally plastic" (p. 306). The reasoning that leads him to this conclusion needs to be understood and contemplated by those who wish to study the genetics of their favorite trait. I strongly encourage those who have not read this book to get a copy and to think deeply about the implications of these models (especially of those in parts III and IV) for their own research.

Weiss warns us not to let "the glamor of finding 'the' gene for a given disease overshadow the greater effort to understand its full causal spectrum" (p. 313). Rather, we need to appreciate that "everything is connected through the evolutionary tree of gene duplication and mutation. We could hardly ask for a more structured subject to study" (p. 314).

This book is divided into four parts: (I) "Genes and Their Expression"; (II) "Introduction to Genetic Epidemiology: Inference from Observational Data"; (III) "Evolution: The Time Dimension in Populations"; and (IV) "Modification of the Inherited Genotype: The Time Dimension in Individuals." In each section, the author uses a healthy mixture of theoretical results and real biological illustrations to make the material accessible and believable to both biologists and statisticians. Clearly, the great strength of this book is in parts III and IV, which are the most closely related to the author's own research interests and thus are the most accurate and most compelling portions of this work.

Many readers who are involved primarily in gene-mapping projects initially will be most interested in reading part II, in which the author discusses the basic technical methods used in the analysis of genetic linkage, segregation, and association. Although these chapters are written in an accessible way, in order to introduce the basic concepts to an uninitiated reader, the author has made a number of overstatements, and some of the details of his claims regarding statistics are not completely accurate. On balance, the pluses outweigh the minuses, for the novice. In a field as dynamic as that of statistical genetics in the past decade, it is nearly impossible to produce a book that describes current methodology accurately. By the time any such book is published, the state of the art will have changed substantially. My own experience as the author of a book about human genetic linkage analysis (Terwilliger and Ott 1994) bears this out. The list of statements that I no longer agree with in my own book is as long as the list of my disagreements with Weiss's claims in this book. This is not a fatal flaw of either book; as with all claims from any author, one generally is advised not to believe anything, unless every premise and logical deduction is understood. In *Genetic Variation and Human Disease,* the logical deductions of the author are stated clearly, and, thus, even novices in the field should be able to evaluate most of the conclusions for themselves. When it comes to unraveling the genetics of complex diseases, none of us can claim to be authoritatively correct: the more strongly an assertion is stated, the more stringently it must be questioned.

The second half of this book should be read and digested by everyone working on mapping genes—from clinicians to molecular biologists to statistical geneticists. Much of the rationale for doing genetic studies in isolated populations is based on classic concepts of evolutionary genetics (see Nevanlinna 1972). Modern concepts of population genetics should be considered now as well, and this book provides a palatable introduction to the issues of greatest concern to human geneticists. There are very serious implications of Weiss's arguments, for these issues. As an example, consider the recent hype that genome screening for linkage disequilibrium and allelic association will be the savior of complex-disease genetics (see Houwen et al. 1994; Risch and Merikangas 1996). I always have been somewhat skeptical of the utility of these methods, for detecting common disease-predisposing alleles, since, if linkage disequilibrium is to be detected, one needs these disease alleles to be identical by descent, in the population. Others have counterargued that, when one detects the so-called disease-predisposing mutation in a candidate gene, one could detect an association with this coding-sequence mutation or with something in disequilibrium with it (see Risch and Merikangas 1996). Extrapolating from the predictions made, in this book, about complex-disease genetics, my skepticism about the utility of genome screening for associations is even greater than it was a priori.

The author starts the third part of this book with a section entitled "(Nearly) Each New Mutation Is Unique" (p. 153). He goes on to explain why there ultimately will be a wide spectrum of many different alleles of each gene, for which the effects on the trait ultimately will vary "somewhat between a Normal and a Laplace distribution" (p. 170). In plant genetics, real-life data from quantitative-trait loci provide tangible support for this model. If this model is accepted, it is clear that every different population will have a different spectrum of several different alleles of different effect sizes, at the same (and at different) loci. Such alleles would be an absolute nightmare to tease apart by allelic association or by measured-

genotype approaches. Thus, even if coding-sequence polymorphisms are detected, their sheer number may reduce drastically the sensitivity of such association studies. Weiss raises many such issues that affect the spectrum of complex-disease genetics, and none of them is resolved fully. I wish that the author had extrapolated more than he has about the ramifications of his evolutionary model on our current approaches to mapping complex disease–predisposing genes and about how we might improve current methods.

There are a great many practical reasons to understand the concepts presented. We are spending millions of taxpayer dollars on the genome screening of many different pedigree or population-based data sets for every potentially genetic trait. Careful review may be needed both to decide if this is a responsible way to spend the money and to identify traits that may be studied most effectively by use of this approach. As the author states, "a few rare alleles at major genes that affect a trait . . . are of little population importance" (p. 313). In the context of the author's prognostications about the large number of different alleles predicted at each locus, one might reconsider whether it is really sensible to invest millions of dollars to develop maps of biallelic markers spanning the genome, for the purposes of disequilibrium analysis. The author advocates thoughtfully planned experiments as the best investment. He writes: "Order can be found in the complexity if we know what to look for. I have tried to suggest that it is in the context of evolution that we are being led to such a synthesis" (p. 314). Drug-company executives contemplating a major investment in the isolation of an array of predisposing alleles of high frequency and weak effect also should consider carefully the arguments raised herein, to evaluate whether their investment is fiscally prudent for each trait that they propose to study. Many other issues are raised indirectly in the book, and readers will finish with different concerns of their own. If a good book is one that provokes the reader to think beyond the printed word, surely this is a book that satisfies that criterion.

Weiss, however, is not entirely pessimistic. Although he both points out many issues that may prove to be stumbling blocks in our efforts to understand the genetic basis of human disease and explains why the "landscape is subtle and complex" (p. 306), he provides reassurance: "Clearly, as mass genotyping technology becomes available, along with a more complete polymorphic map, we will be able to document an increasing fraction of the alleles that have consistently strong effects" (p. 306). Although these rare alleles of strong effect do not explain much of the general population variability in which Weiss is primarily interested, as Weiss does admit, these identifiable alleles ultimately will be of "great biomedical importance" (p. 313).

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Gene Therapy: A Primer for Physicians. 2d ed. By Kenneth Culver. Larchmont, NY: Mary Ann Liebert, Inc. Pp. 216. $59.00.

Human gene therapy has grown exponentially over the past decade and has expanded into a field including well over 100 clinical trials. As the number of trials has grown, so has the need for practicing physicians to understand gene therapy, in order to be able to guide their patients. This book provides a unique resource, since it attempts to educate both the physicians and the patients who may be interested in participating in gene therapy trials. The second edition includes expanded discussions of genetic diagnosis and gene therapy technologies and provides updated information in the appendices. The book begins with a brief introduction to the development of recombinant DNA and gene therapy technology, followed by the methods used for gene transfer/gene therapy. The second section focuses on individual diseases and the techniques used to treat them with gene therapy. The bibliographies are extensive and include many of the most useful primary references. However, the choice of topics seems somewhat arbitrary. Whereas the author stresses the importance of identifying disease genes, he gives less attention to the fundamental technical challenge in gene therapy—that is, how to transport a large, highly charged molecule (i.e., DNA) into the cell nucleus. A welcome addition would be a table comparing and contrasting the efficiency of the various techniques and vectors available for the transduction of cells in culture or in vivo. There are a few inaccuracies; for example, in the section on cancer gene therapy, the description of "sensitivity" enzymes, which would render a cell susceptible to chemotherapy (e.g., thymidine kinase/ganciclovir treatment), omits several important enzymes and misstates the relative potencies of different systems. The section on ethical issues in gene therapy is quite short but does highlight the major points.

The third section includes appendices, which include some extremely useful, as well as some irrelevant, information. The list of resources for further information (appendix A) could be far more inclusive, and the appendix entitled "Points to Consider" (appendix E), which describes the requirements for Recombinant DNA Advisory Committee submission of protocols, is of limited interest to the intended audience. The index linking health disorders to chromosomal locations (appendix D) is only relevant to individuals interested in the efforts to map the human genome; this index might have been improved by the linkage of health disorders to specific disease genes and by the inclusion of relevant references. The well-organized, but slightly outdated, list of currently approved gene therapy trials and contact people (appendix B) is