Book Reviews

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Mouse Genetics. By Lee M. Silver. New York: Oxford University Press, 1995. Pp. 368. $55.00.

What is the difference between an inbred strain and an outbred stock? What about congenic and isogenic strains? Why are LOD scores not used to determine a gene map location for mice, and what does one do with a strain distribution pattern? Is it better to use a backcross or an intercross for positional cloning? Answers to these questions and more are found in the monograph *Mouse Genetics,* which is deceptively slim yet contains a wealth of information for both the novice and the enthusiast.

After an informative and occasionally whimsical introduction, *Mouse Genetics* contains nine chapters: three chapters explain different types of strains and their applications, one considers techniques and uses of mutagenesis and transgenesis, and the remaining five discuss genomics and gene mapping. The book is eminently readable and strikes an ideal balance between historical references and practical applications. Recombinant inbred (RI) strains, for example, are described simply and clearly, beginning with Donald Bailey's interest in complex traits and ending with an explanation of how RI strains can be used to determine whether variable expressivity is caused by polygenic inheritance. Although genetics is emphasized more than embryology, advances in both disciplines are responsible for the favored status held by mice, in biomedical research. This underlying theme is present throughout the book as Silver discusses various topics, such as the reproductive and ovulatory characteristics of specific strains and their F1 hybrids.

Nearly anyone interested in genetics will enjoy reading, and will benefit from, the chapters devoted to the origins of inbred and wild-derived strains, which contain such useful information as the relationships between C57BL/6 mice from different suppliers, the number of generations "required" to make an inbred or a congenic strain, and the nomenclature used to describe subspecies, strains, and mutations. The architecture of the mouse genome is described clearly and succinctly in a single chapter, and the human genome is used as a frequent frame of reference, as in, for example, the description of the different types and distributions of repetitive DNA elements. The chapter on linkage analysis is not quite 70 pages, yet it manages to cover key concepts with surprising depth. In particular, RI strains, interspecific backcross mapping panels, elementary statistical considerations (including a prior-probability correction for genome scans), and approaches to the analysis of complex traits are presented in sufficient detail, so that most practitioners will find exactly what they need. Although written mostly in 1993, it is quite up-to-date and includes, for example, DNA pooling strategies for the identification of linked markers, potential applications of radiation hybrid mapping to mouse genetics, and a brief discussion of techniques for the engineering of subtle changes in the genome, by use of embryonic–stem cell technology.

What's missing from *Mouse Genetics*? Perhaps there should be more about X inactivation and the structure of the sex chromosomes, because of, in part, the unique role that mouse genetics has played in the understanding of these processes (e.g., Searle's and Cattanach's "translocations") and because, in part, human geneticists stand to benefit from this understanding. In addition, I would have enjoyed reading more about examples and mechanisms of segregation distortion; ironically, there is much more about the *t*-test than the *t*-complex.

Mouse Genetics is not a laboratory manual for experimental embryology, as is *Manipulating the Mouse Embryo,* nor is it an encyclopedic reference, as is *Genetic Strains and Variants of the Laboratory Mouse*. Instead, *Mouse Genetics* contains the essential principles necessary to understand and to devise experiments in which mouse genes play a central role. The book is directed at readers who are already familiar with molecular biology and with fundamental genetic principles (although not with statistics) and will be accessible to biologists in any field. It will be especially helpful to the human geneticist who wishes to understand a journal article or to write a research grant or who just wants to learn more about a furry model organism. This is not to say that *Mouse Genetics* is not for mouse geneticists. On the contrary, the two copies in my laboratory are a favorite of students at all levels. In the preface, Silver states that the book was written to answer questions posed by new stu-

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-