GENETICS AND PROBABILITY IN ANIMAL BREEDING EXPERIMENTS

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A primer and reference book on probability, segregation, assortment, linkage and mating systems for biomedical scientists who breed and use genetically defined laboratory animals for research

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Dedicated to

THE JACKSON LABORATORY,
founded in 1929;
to its founder,
a man of vision;
and to its people,
past, present, and future;
on the occasion of its fiftieth anniversary in 1979

Preface

For nearly 20 years, I was Director of the Jackson Laboratory in Bar Harbor, Maine, one of the world's centres for research in mammalian genetics. During most of those years, I gave a series of lectures on genetics and mouse breeding to each year's new crop of staff members and postdoctoral fellows. This book is an expanded version of those lectures. It is intended to be useful to research workers who are just starting to work with genetically defined animals, such as mice of various inbred strains, and who need an introduction to the probability aspects of transmission genetics in order to enrich their understanding of the kinds of animals already available and to guide them in the design and analysis of their own breeding experiments.

The new staff members and postdoctoral fellows I dealt with had many different formal educational backgrounds. They included physiologists, biochemists, embryologists, psychologists, pathologists, immunologists, microbiologists and physical chemists. The yearly group also included geneticists, but contemporary geneticists are of many kinds: cytogeneticists, behavioural geneticists, biochemical geneticists, physiological geneticists, immunogeneticists, developmental geneticists, radiation geneticists and quantitative geneticists. All of these kinds of scientists usually have a working knowledge of the classical principles of heredity and of the classical methods of statistical inference. Yet, except for the quantitative geneticists, they usually feel uneasy with the probability aspects of transmission genetics and with the methods of statistical inference for discrete variables.

Scientists of this sort will soon encounter the folkways and jargon of the geneticists who breed laboratory animals. They will want to know, and will need to know: how new genes are discovered, how one establishes that a new gene is not like any already known gene, how one finds the position of a new genetic locus on the chromosome map, how alike are the animals of an inbred strain, how many generations of breeding does one have to arrange to ensure a given probability of alikeness, how many matings should one make up and how many progeny per mating should one observe in each generation when perpetuating a recessive mutation? Answers to questions of this sort will be found in the following pages.

This book is intended, in two ways, to meet the needs of research workers who use laboratory animals: first, as a coherent self-contained account of the probability

and statistical aspects of laboratory animal breeding and, second, as a ready reference book for terminology and formulae. The organisation of the book reflects these two objectives. To provide an account, the reader is conducted through five model breeding experiments of the sort that he, himself, may soon want to carry out in his own research. To provide a ready reference, the more useful formulae are assembled in tables or, otherwise, are identified by serial numbers within chapters.

I am assuming that everyone who reads this book knows that the units of heredity are called *genes* and that genes are located on *chromosomes*. I am also assuming that everyone knows about the elementary principles of transmission genetics: *segregation of alleles* and *assortment* or *recombination of non-alleles*; and that the genetic phenomena of segregation and assortment exactly parallel the chromosomal phenomena of *disjunction, assortment* and *crossing-over* during germ-cell formation. The book deals with various modifications and complexities of these elementary principles of transmission genetics. It does not deal with the molecular nature of the gene, nor with how genes replicate or how they make proteins, for these aspects of physical, physiological, developmental and biochemical genetics are not relevant to its purpose.

I am further assuming that the reader's background in the probability aspects of genetics is skimpy at best, even though he or she is familiar with the 1:1 and 1:1:1:1 segregation ratios of backcrosses and the 3:1 and 9:3:3:1 segregation ratios of intercrosses for one and two loci. Such readers should find many familiar concepts of a first course in genetics recast in a more sophisticated symbolism of probability and thereby put into forms that lead to symbolic predictions and bases for statistical inferences about the outcomes of breeding procedures. Even so, the reader's level of mathematical competence need not exceed algebra. All manipulations requiring calculus have been relegated to appendices.

The book is intended to be read, to be studied and to be used as a reference. Yet it is not cast in the form of a textbook. I have tried to compensate for this deliberate omission by including numerous worked examples in the text. Beyond that I suggest that for such exercises the interested reader should procure elementary textbooks on probability and statistics and on experimental genetics, of which there are dozens of good ones now available.

As a convenience in exposition and as a reflection of my own first-hand familiarity, I have referred to *mice* throughout the text. Yet the concepts and methods described in the book are applicable to any bisexual organism whose reproductive pattern is similar to that of mice. This includes all the common laboratory mammals: rats, guinea pigs, hamsters, rabbits, gerbils, nutria, cats and dogs.

This book deals with the overlap of the domain of genetics and the domain of probability. To pursue that figure of speech just a bit further: each domain has some lofty peaks and some profound caverns. To ascend the peaks or to explore the caverns would require special hand tools and foot gear. Our explorations will, instead, be confined to the gentle paths among the foothills between the domains, with short excursions into a few nooks and crannies. Soft-soled shoes and hand-held calculators are all we shall need.

The first chapter is composed of extremely condensed statements about the

concepts of probability needed for genetic predictions and the methods of statistics needed in the analysis of genetic data. My emphasis is on the meaning and use of the numerous concepts and methods needed by the laboratory animal breeder. Biologists who feel repelled by statistical notation may prefer to skim this chapter at first reading and refer to it only when a particular idea in a later chapter depends upon a formula in chapter 1.

Chapters 2 and 3 are devoted to deriving Mendel's principles of heredity from the data of a few mouse breeding experiments, but with emphasis on full probability statements of these principles rather than upon the ratios of more elementary treatments.

Chapter 4, on linkage, is like chapters 2 and 3, on segregation and assortment, in putting the concepts in probability form. Chapter 5 does the same thing for various regular systems of mating in widespread use, but also uses the probability results to predict the genetic consequences of using the systems over many generations.

The appendices are essential for the serious breeder of laboratory animals, both for extensions of the theoretical aspects and the practical problems he will face. Appendices 1-7 contain technical details that I thought should be removed from the text because they require more mathematical preparation than I am assuming for most of the users of this book. They are, however, an invitation to the reader to delve a little deeper into the fascinating topics of linkage estimation and of analysis of mating systems. Appendix 7 deals with the practical problems of how many animals to raise and how many matings to make up for various mating systems described in chapter 5. Appendices 8, 9 and 10 deal with the intensely practical problems of nomenclature of genes and strains of mice, of a record-keeping system for breeding laboratory animals, and of mouseroom layout and operation.

The elaboration of the principles of transmission genetics is largely the work of Sewall Wright, R. A. Fisher and J. B. S. Haldane, along with those who followed in their wake. I have not given references to the origin of each probability and statistical statement in this elementary introduction. The formulae, or the fundamental relationships from which they are derived, can be found in the vast writings on genetics, probability and statistics in the middle two quarters of this century. I have, however, given references to various contemporary sources of general information about genetics, probability and statistics and to specific recent developments cited in the text.

I am indebted to several people for direct encouragement with respect to the preparation of this book. My thanks are especially due to my wife, Margaret C. Green, and to my former colleagues at the Jackson Laboratory, Donald W. Bailey and Robert L. Collins, for reading the text critically during its preparation. My thanks are also due to Randall C. Adams for carrying out the computations used for the figures in chapter 5.

Bar Harbor Earl L. Green

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