METHODOLOGY *in* MAMMALIAN GENETICS

WALTER J. BURDETTE

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Edited by

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PREFACE

Information recently acquired about the biochemistry of heredity has increased the likelihood of determining precisely how the more formal transmission of genetic information is accomplished in higher organisms and has imposed the obligation to renew the task of controlling changes in composition, propagation, and action of the genetic material. The complexity of mammalian genesis and development is regarded no longer as a barrier to investigation at the molecular level, but more as an opportunity to study mechanisms that do not exist in lower organisms in relation to common hereditary units and to choose between alternate explanations for a given process. Possibly the greatest advantage the laboratory mammal offers is not only the possibility of developing strains of animals having remarkably similar partial or total genome but also the opportunity to breed representatives from diverse strains in a manner appropriate for the elucidation of genetic mechanisms. In addition, these uniform lines are available for comparison of the genetic behavior of cells with known properties *in vivo* and *in vitro*. Recent evidence for fusion of mammalian cells *in vitro* suggests that the analytical advantages of sexual reproduction may be extended to studies of the somatic cell as well. Also, the many hereditary diseases known to occur in inbred mammals and the varied response of different strains to bacterial, viral, and parasitic inoculation offer means to determine parameters that may also be operable in similar diseases in man.

A host of methods have been evolved for providing stocks of mammals with uniform genotype suitable for given experimental objectives. The theoretical and practical aspects of insuring this type of control and some indication of how methodology from other scientific disciplines may be used in mammalian genetics are mandatory for an approach to the solution of problems that engage the attention of many contemporary investigators. The intent of the contributors to this volume is to provide a selected array of methods applicable to mammalian genetics that may prove useful

in implementing the ideas of those striving to solve the intricate problems encountered in investigations concerned with differentiation, homotransplantation, directed mutation, repair of deleterious mutants, genetic determinants in disease, and the like.

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CONTENTS

GENETIC STOCKS AND BREEDING METHODS

E. L. Green, Ph.D., and D. P. Doolittle, Ph.D.

SYSTEMS *of* MATING USED *in* MAMMALIAN GENETICS†

Mammalian geneticists use a variety of mating systems, each designed to accomplish a specific purpose. To use the systems effectively, it is necessary to know what each system is, when it can be used, and what its theoretical genetic consequences are. This paper describes seven systems of mating which have passed into general use by mouse geneticists. Each system will be described by means of its mating types and their probabilities through successive generations. In some cases reference will be made to the kinds of genotypes and their probabilities, in particular to the probability of heterozygotes.

The theory of systems of matings has been extensively developed by Wright,[1442] Bartlett and Haldane,[56] and Fisher,[375] on whom we have drawn heavily for this exposition. The system later called the "cross-backcross-intercross system" has not been analyzed heretofore; its theoretic consequences are presented here for the first time. We are indebted to Dr. George D. Snell who described the system to us and who has been the first to use it.

The following sections outline the analysis of the mating systems after first defining some necessary symbols and describing the general steps of the analytical method. The last section suggests a few practical rules for the breeders of laboratory animals who desire to improve the genetic quality of mice, rats, rabbits, and other mammals for research.

† The authors gratefully acknowledge the support of the Sagamore Foundation and the Richard Webber Jackson Memorial Fund.

NOTATIONS AND DEFINITIONS

Three autosomal loci of diploid, sexually reproducing organisms such as mice will be designated by the symbols: *a*-locus, *D*-locus, and *r*-locus. The *a*-locus is any locus whose heterozygosity is in question as a given breeding system advances from generation to generation. The *D*-locus is the locus of a dominant mutation; the *r*-locus, that of a recessive mutation. The *D* and *r* mutations are called the genes of interest. The alleles at these three loci will be denoted as *A*/*a*, *D*/*d*, and *R*/*r*, and the genotypes by *AA*, *Aa*, *aa*; *DD*, *Dd*, *dd*; and *RR*, *Rr*, *rr*. The relative frequency (i.e., probability) of *Aa* will be denoted by *h*.

The mating types are of four kinds:

Incrosses: $AA \times AA$ and $aa \times aa$, matings of like homozygotes,
Crosses: $AA \times aa$, matings of unlike homozygotes,
Backcrosses: $AA \times Aa$ and $aa \times Aa$, matings of homozygote and heterozygote,
Intercrosses: $Aa \times Aa$, matings of heterozygotes.

When the terms incrosses, crosses, backcrosses, and intercrosses appear in lower-case letters, they refer to the locus with questionable heterozygosity. When they appear in small capitals, INCROSSES, CROSSES, BACKCROSSES, INTERCROSSES, they refer to the locus of interest. The last three of these terms are in general use.

The relative frequencies or probabilities of the mating types will be denoted by $p, q, r, \ldots, v$ with the definition varying slightly from system to system. In general, p will be used to denote the frequency of incrosses ($AA \times AA$ and $aa \times aa$), the maximizing of which is the objective of all of the systems of breeding, except random mating. A subscript n (or m) denotes generation n (or cycle m). G (or C) will stand for generation (or cycle). **G**, **P**, **A**, etc. are matrices. P will designate probability.

The probability of crossing over between the *a*-locus with questionable heterozygosity and the *D*- or *r*-locus carrying the mutation of interest will be denoted by c. To avoid a troublesome complication in notation, for any two loci, c will be treated as equal in the two sexes.

The probability of heterozygosity at the *a*-locus in generation n (or cycle m) will be denoted by h_n (or h_m). In all cases, as p_n increases, h_n decreases. As will be seen, h_n is a function of the probabilities of backcrosses and intercrosses in each system of mating.

SYSTEMS OF BREEDING

Relatively few of the systems developed by breeders of domestic and laboratory mammals are used frequently enough to warrant exposition here. Parent-offspring inbreeding, line breeding, or systems which use first, second, or third cousins will not be described. The systems included are, with the exception of random mating, all regular systems which permit the development of sequence equations to relate the probabilities of incrosses, etc., of one generation to those of the next. Irregular