ESTIMATION OF NONADDITIVE HEREDITARY VARIANCE IN TRAITS OF MICE¹

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THE choice of efficient breeding procedures for the genetic improvement of a population is contingent upon knowledge of the relative magnitudes of the components of hereditary variance—additive, dominance, and epistatic—for the characteristic in which improvement is sought. Considerable evidence regarding the extent of additively genetic variance is available for many traits in animals. However, the relative importance of the nonadditive portion of the hereditary variance is often unknown.

Inbred lines of large animals are difficult to obtain and those available may possess only a moderate degree of homozygosity. Hence, noninbred material alone may have to be employed in experiments designed to measure the extent of nonadditive hereditary variance. Two problems are encountered in the use of random-mating populations for this purpose. First, it is necessary to assess adequately fluctuations in environmental conditions which may occur during a long-term experiment. Secondly, the sampling variance of estimates will be large because the coefficients of the components of hereditary variance are small in the covariances among relatives from noninbred parents.

ESTIMATION PROCEDURES

The basis for estimating nonadditive hereditary variance in random bred material is the comparison of full-sib and half-sib covariances. Using the notation of COCKERHAM (1954), and assuming inbreeding of parents to be zero,

$4(\text{Cov FS}) - 8(\text{Cov HS}) = \sigma_{01}^2 + (1/2)\sigma_{20}^2 + (1/2)\sigma_{11}^2 + (1/4)\sigma_{02}^2 + (3/8)\sigma_{30}^2 + (1/4)\sigma_{21}^2 + \dots$, where σ_{01}^2 is the dominance variance and the remaining components comprise the epistatic variance.

BYWATERS (1937) and CHAPMAN (1946) employed this procedure in studies of swine and rats, respectively. Paternal half-sibs are relatively abundant in animal populations but full-sib data are rare. However, the principal disadvantage of this method is that environmental fluctuations may not be adequately controlled. This is especially true if the data are collected from breeding records

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of flocks or herds over a period of years, rather than from a designed experiment. In addition, maternal influences may be important and the use of the factors *four* and *eight* in estimating the full extent of the dominance component means that the variances of the estimates are increased by the squares of these factors.

The method of "diallel mating" has often been used to estimate nonadditive hereditary variance in random-mating populations of poultry (e.g., LERNER 1945; HAZEL and LAMOREAUX 1947; and KAN, KRUEGER and QUISENBERRY 1959). All possible combinations of matings are made among m males and d females. The male-by-female interaction component of the factorial analysis is used to estimate the nonadditive hereditary variance. The difficulty with this procedure is that normally a female can produce offspring by only one male at a given mating. Therefore, to describe fully the situation, effects associated with time must be introduced into the model as follows:

$$Y_{ijk} = \mu + s_i + m_j + (sm)_{ij} + f_k + (sf)_{ik} + (mf)_{jk} + (smf)_{ijk},$$

where

s_i is an effect common to all observations in the i th series, hatch, or mating period,

m_j is an effect peculiar to all offspring by the j th male parent

$(sm)_{ij}$ is an effect peculiar to all offspring by the j th male in the i th series,

f_k is an element common to all progeny of the k th female parent,

$(sf)_{ik}$ is an interaction effect peculiar to offspring of the k th female parent in the i th series,

$(mf)_{jk}$ is an interaction element present for all offspring of the k th female and the j th male parents, and

$(smf)_{ijk}$ is an effect common to progeny of the k th female and the j th male parents in the i th series.

All elements with the exception of μ are assumed to be independent random variables with zero means and variances σ_s^2 , σ_m^2 , σ_{sm}^2 , σ_f^2 , σ_{sf}^2 , σ_{mf}^2 , and σ_{smf}^2 , respectively. The assumption that the s_i are random may be debatable; however, one can conceive of a very large population of temporal effects. The biological interpretation of the elements in the above model will be given in a later section.

Diallel Design I is outlined in Table 1 and the usual form of the analysis of variance is given in Table 2 for the case where each mating results in one offspring.

Using M_3 as the estimate of σ_{mf}^2 the bias is $(\sigma_{smf}^2 + \sigma_{sf}^2)$. An unbiased estimate of the female component of variance $(1/m)(M_2 - M_3)$ is given by this design. Complete confounding of males and series means that σ_s^2 , σ_m^2 , and σ_{sm}^2 cannot be disentangled.

The factorial array of diallel matings can be achieved by mating only a portion of the females to each male in a given mating series. Diallel Design II where each male appears in every series of matings is given in Table 3.

In Table 3, each D_m represents a group of d/m randomly chosen female parents. Table 4 gives the analysis of variance for Diallel Design II when one offspring results from each mating.

TABLE 1
Mating plan for Diallel Design I

Series	Matings
	Male 1
1	$D_1 D_2 \dots D_d$
	Male 2
2	$D_1 D_2 \dots D_d$
.	.
.	.
.	.
	Male m
m	$D_1 D_2 \dots D_d$

TABLE 2
Analysis of variance for Diallel Design I

Source	df	MS Code	E(MS)
Series and males	$m-1$	M_1	$\sigma_{smf}^2 + \sigma_{sf}^2 + \sigma_{mf}^2 + d(\sigma_s^2 + \sigma_m^2 + \sigma_{sm}^2)$
Females	$d-1$	M_2	$\sigma_{smf}^2 + \sigma_{sf}^2 + \sigma_{mf}^2 + m\sigma_f^2$
Series and males $\times$ females	$(m-1)(d-1)$	M_3	$\sigma_{smf}^2 + \sigma_{sf}^2 + \sigma_{mf}^2$

TABLE 3
Mating plan for Diallel Design II

	Male 1	Male 2	Male m
Mating Series 1	D_1	$D_2 \dots D_m$	
Mating Series 2	D_m	$D_1 \dots D_{m-1}$	
.	.	.	.
.	.	.	.
.	.	.	.
Mating Series m	D_2	$D_3 \dots D_1$	

As an estimate of σ_{mf}^2 , V_5 is biased by the sum $\sigma_{smf}^2 + \sigma_{sf}^2$. If it is not reasonable to assume σ_{smf}^2 and σ_{sf}^2 to be negligible, this design is inappropriate for the estimation of σ_{mf}^2 . Diallel Design II is more appropriate for the estimation of breeding values of males as suggested by KUDRJAWEZ (1934). However, the comparison of breeding values may be influenced by any interactions involving series.

A design contrived to provide an unbiased estimate of σ_{mf}^2 , Design III, is presented in Table 5. The letters $F_1, F_2, \dots, F_m$ each represent groups of equal size from a total of n_1 randomly selected females, and $F_{m+1}, F_{m+2}, \dots, F_{2m}$ each

TABLE 4
Analysis of variance for Diallel Design II

Source	df	MS Code	E (MS)
Series	$(m-1)$	V_1	$\sigma_{smf}^2 + \sigma_{sf}^2 + \sigma_{mf}^2 + \frac{d}{m} \sigma_{sm}^2 + d \sigma_s^2$
Males	$(m-1)$	V_2	$\sigma_{smf}^2 + \sigma_{sf}^2 + \sigma_{mf}^2 + \frac{d}{m} \sigma_{sm}^2 + d \sigma_m^2$
Series $\times$ Males	$(m-1)^2$	V_3	$\sigma_{smf}^2 + \sigma_{sf}^2 + \sigma_{mf}^2 + \frac{d}{m} \sigma_{sm}^2 + \frac{m}{m-1} \sigma_f^2$
Females in same Series-male	$m(\frac{d}{m}-1)$	V_4	$\sigma_{smf}^2 + \sigma_{sf}^2 + \sigma_{mf}^2 + m \sigma_f^2$
Series $\times$ Females in same Series-male	$m(m-1)(\frac{d}{m}-1)$	V_5	$\sigma_{smf}^2 + \sigma_{sf}^2 + \sigma_{mf}^2$

TABLE 5
Design III mating plan

	Male 1	Male 2	Male 3	Male m
Series 1	F_1, F_{m+1}	F_2, F_{m+2}	F_3, F_{m+3} . . .	F_m, F_{2m}
Series 2	F_1, F_{2m}	F_2, F_{m+1}	F_3, F_{m+2} . . .	F_m, F_{2m-1}
.				
.				
.				
Series m	F_1, F_{m+2}	F_2, F_{m+3}	F_3, F_{m+4} . . .	F_m, F_{m+1}

represent groups of equal size from a total of n_2 females chosen at random. The former group of female parents is referred to as the “not-switched” groups and the latter as the “switched” groups. Thus mn_1 females are repetitively mated to the same males in each series of matings, and mn_2 females are mated to different males in each series of matings.

Some features of this design should be noted. It is actually a composite of two designs, a nested design in which each male has F_i different mates each mated m times, once in each series, and a Diallel Design II in which the males exchange their mates in the m series of matings. The same males are used across both phases, but the dams represent a dichotomy of mating categories—those which are repeat-mated to the same male, and those which are mated to different males in the subsequent series.

The analysis of variance for Design III is presented in Table 6 for the situation where one offspring results from each of the $m^2(n_1 + n_2) = m^2N$ matings. In Table 6 “Groups” refer to the two classifications of females: those which always

TABLE 6
Analysis of variance of Design III

Source	df	MS Code	E(MS)					
			$\sigma_{smf}^2 + \sigma_{sf}^2$	σ_{mf}^2	σ_f^2	σ_{sm}^2	σ_m^2	σ_s^2
Series	$m-1$	V_1	1	n_2/N		N		mN
Males	$m-1$	V_2	1	$\frac{mn_1 + n_2}{N}$	$\frac{mn_1}{N}$	N	mN	
Series $\times$ males	$(m-1)^2$	V_3	1	n_2/N	$\frac{mn_2}{N(m-1)}$	N		
Groups	1	V_4	1	$\frac{mn_2 + n_1}{N}$	m			
Series $\times$ groups	$m-1$	V_5	1	n_1/N				
Males $\times$ groups	$m-1$	V_6	1	$\frac{mn_2 + n_1}{N}$	$\frac{mn_2}{N}$			
Series $\times$ males $\times$ groups	$(m-1)^2$	V_7	1	n_1/N	$\frac{mn_1}{(m-1)N}$			
Females in males	$m(n_1-1)$	V_8	1	m	m			
Series $\times$ females in males	$m(m-1)(n_1-1)$	V_9	1					
Females in same SM	$m(n_2-1)$	V_{10}	1	1	m			
Series $\times$ females in same SM	$m(m-1)(n_2-1)$	V_{11}	1	1				

retain the same mates *vs.* those which rotate mates. Of the estimators available from Table 6, the following are of interest:

$$(\sigma_{mf}^2)_1 = (V_{11} - V_9)$$

$$(\sigma_{mf}^2)_2 = (V_8 - V_{10})/(m-1)$$

It can be shown (MILLER 1962) that the 11 mean squares of Table 6 can be reduced to six by combining mean squares whose expected values involve the same components. In this way estimates of the six components are obtained (σ_{smf}^2 and σ_{sf}^2 can only be estimated jointly).

EXPERIMENTAL PROCEDURE

Design III was employed to estimate the extent of nonadditive hereditary variance in certain traits of a random-mating population of the house mouse, *Mus musculus*. This population is maintained as the control in a selection experiment for growth and maternal performance. The control line, derived from a cross of four inbred lines (A/Jax, AKR, BALB/C, DBA/2), is maintained each

generation by mating two females to each of 15 males. One male and one female are chosen at random from each paternal half-sib family and each full-sib family, respectively.

The following traits were studied in the present experiment: the number of mice born in a litter (Y_1), the weight of a standardized litter of six mice at 12 days of age (Y_2), individual weight at three weeks of age (Y_3), individual weight at six weeks of age (Y_4), and the individual gain in weight from three to six weeks of age (Y_5).

Design III was employed in replication over both time and space for the case of $m = 2$. Two replications over time were necessary due to limited cage facilities.

In the first replication males were chosen at random and each was mated to five females. Mates were assigned at random except that sib mating was avoided. The details of handling and measurement of the animals have been given by COX, LEGATES, and COCKERHAM (1959), YOUNG (1961), and MILLER (1962). All surviving female offspring resulting from the matings were retained and mated at the age of ten weeks to randomly chosen male offspring of the first matings. The matings were made at the rate of one male to four females. The number of mice at birth and the weight at 12 days of the resulting litters were obtained, thus completing the first *series* of matings for this replication.

The second series of matings was made when the parental animals were approximately 19 weeks of age. Only parents with surviving litters from the first series of matings were used. Parents were assigned to replication mating units ("sets") subject to these restrictions: (1) two males which had the same number of mates with surviving first litters were assigned to the same set; (2) full brothers and half brothers were not assigned to the same set; (3) where possible the number of mates switched (n_2) and not switched (n_1) per male were made equal; when this was not possible, n_2 was made greater than n_1 by the difference of one animal. The data were gathered from the resulting litters similarly to the procedure for the first matings.

The second replication was initiated using the unselected progeny of the first series of matings after all the required data had been gathered. This resulted in an economy of labor and facilities since all female offspring from the first matings had to be mated in order to obtain measurements on their litters. These matings were made at the ratio of one male to four females; otherwise, the procedure was the same as for the first replication.

RESULTS AND DISCUSSION

One objective of this work was to provide an idea of the merit of the experimental design from the standpoint of practical application. Table 7 provides a summary of the losses of the 110 female parents during the course of the experiment. The summary of replicate two is not comparable to that for replicate one because all female parents selected for the former had litters which were 12 days of age when the replicate was in fact initiated. The proportion of females with no first litters is much higher than is experienced in the regular colony where the mating ratio is one male to two females.

TABLE 7

Number of original female parents lost in course of the experiment

Reason for loss	Number of females	
	Replicate I	Replicate II
No first litters	53	..
First litter died	7	..
Dam died before weaning first litter	7	4
Dam died prior to second littering	1	..
No second litters	7	14
Second litter died	3	4
Dam died before weaning second litter	1	2
Eliminated due to incomplete sets	3	4
	82	28

The values in Table 7 are based to some extent upon arbitrary standards imposed with respect to the nonorthogonality permitted in subclass frequencies. The restriction was imposed that a female parent must have had a surviving litter in both series of matings in order to be included in the experiment. In addition the requirement was made that all series-male subclasses had to be filled, considering the switched and non-switched segments separately, in order for the set in question to be used. These requirements resulted in discarding data from some females which had surviving litters in each series. Table 7 applies only to the individual growth measurements; losses were more extreme for the litter measurements.

In order to reduce non-genetic variability, two types of adjustments to the data were made. The 12-day weights of the small number of litters with less than six mice at 12 days were multiplied by the factor $6/N$ where N is the number of survivors at 12 days. The six-week weights were adjusted for sex by a multiplicative procedure presented by FALCONER and KING (1953).

The means and standard deviations of the various traits are presented in Table 8. The weight measurements are expressed in grams.

The degrees of freedom for the within-set mean squares are given in Table 9. These are listed separately for each of the analyses performed. The most striking feature is the inequality in degrees of freedom among mean squares, especially the predominance of the within-litter comparisons.

TABLE 8

Means and standard deviations of variables

Trait	Number	Mean	S.D.
Number born (Y_1)	1161	8.08	2.30
12-day litter wt. (Y_2)	986	38.40	6.36
3-week wt. (Y_3)	2879	9.51	1.59
6-week-wt. (Y_4)	2879	21.28	2.29
Postweaning gain (Y_5)	2879	11.77	1.65

TABLE 9

Degrees of freedom for analyses involving the different combinations of variables

Source	Degrees of freedom		
	$Y_3Y_4Y_5$	$Y_1Y_3Y_4Y_5$	$Y_1Y_2Y_3Y_4Y_5$
Between sets, within replicate	40	40	40
Within sets:			
Series	42	42	42
Males	42	42	42
Groups	39	34	30
Series $\times$ males	42	42	42
Series $\times$ groups	39	34	30
Males $\times$ groups	39	34	30
Series $\times$ males $\times$ groups	39	34	30
Females in males	28	23	19
Series $\times$ females in males	28	23	19
Females in SM	64	56	52
Series $\times$ females in SM	64	56	52
Within litters	2,371	699	556

The estimates of components of variance given in Table 10 were derived as described by MILLER (1962). Unequal numbers in the various subclasses required a more involved procedure than that indicated in Table 6: (1) mean squares were equated to their expected values, (2) the error component estimated from the among-full-sib mean square was subtracted from each mean square, and (3) a least-squares analysis of the remaining unweighted within-set mean squares was performed to obtain estimates of components.

The component σ_{mf}^2 is the item of principal interest in Table 10. If we assume that the only reason that the contributions of male and female parents are not

TABLE 10

Estimates of components of variance

Trait	σ_e^2	$(\sigma_{smf}^2 + \sigma_{sf}^2)$	σ_{mf}^2	σ_f^2	σ_{sm}^2	σ_m^2	σ_s^2	Sum of components
Components of variance								
Number born (Y_1)	4.52	0.50	0.39	-0.41	0.13	0.28	-0.01	5.40
12-day litter wt. (Y_2)	27.99	1.84	-0.86	1.47	-0.21	0.70	1.46	32.39
3-week wts. (Y_3)	0.56	1.07	-0.34	0.50	-0.02	0.13	1.40	3.30
6-week wts. (Y_4)	2.65	1.70	-0.79	0.81	0.12	0.28	0.93	5.70
Postweaning gain (Y_5)	1.85	0.76	-0.10	0.13	0.02	0.07	-0.08	2.65
Components as percent of total*								
Y_1	78	8	7	0	2	5	0	
Y_2	84	6	0	4	0	2	4	
Y_3	15	29	0	14	0	4	38	
Y_4	41	26	0	13	2	4	14	
Y_5	65	27	0	5	0	3	0	

* Negative estimates considered zero in computing percentages.

reflected in an additive manner in the offspring is the interaction of allelic and non-allelic genes, σ_{mf}^2 has expectation

$$1/4 \sigma_{01}^2 + 1/8 \sigma_{20}^2 + 1/8 \sigma_{11}^2 + 1/16 \sigma_{02}^2 + \dots$$

It must be pointed out that σ_{mf}^2 may contain a bias if genes transmitted to the offspring by the male parent interact with a maternal effect provided by the mother. BRUMBY (1960) reported an interaction of genotype of the young with maternal environment of the mother for body weight in mice. The data of COX *et al.* (1959) indicated the possibility of an effect of this nature in pre-weaning weights of mice. YOUNG (1961) found little evidence for genotype-maternal environment interactions in traits of mice.

Negative estimates of σ_{mf}^2 were obtained for all traits except number born where seven percent of the total variance was attributable to gene interactions. An estimate of all the dominance variance plus some fraction less than one half of the possible epistatic variance is given by $4(\sigma_{mf}^2)$. Hence, for number born, this gives an estimate of 28 percent of the total variance being due to nonadditive genetic effects.

In general, traits closely related to reproductive fitness tend to exhibit a greater proportion of the total hereditary variance as nonadditive than do traits less related to fitness (FALCONER 1960a). An estimate of this proportion for number born is

$$\frac{\sigma_{mf}^2}{\sigma_{mf}^2 + \sigma_m^2} = 0.58.$$

FALCONER (1960b) reported evidence for dominance variance in number born in a litter of mice on the basis of observed inbreeding depression. A linear decrease of approximately one-half offspring per ten percent increase in the inbreeding coefficient was obtained in a series of full-sib mating experiments. Indications were found that genes acting upon the prenatal viability of the young and genes affecting fertility of the mother were roughly of equal importance to the response observed.

The negative values obtained for the remaining four traits are interpreted as resulting from sampling about some true value of σ_{mf}^2 of zero or near-zero. The extremely large negative values obtained for 12-day litter weight, weaning weight and six-week weight, are indicative of the large sampling variability of σ_{mf}^2 .

Additive hereditary variability is reflected by both the components σ_f^2 and σ_m^2 . Since variation arising from maternal effects is also contained in σ_f^2 , the difference between these components is presumed to reflect the contribution of the mother through the maternal environment provided the young. Estimates of heritability (based on σ_m^2) and the proportion of maternal effects variance for the various traits are presented in Table 11.

That the trait most intimately related to reproductive fitness exhibited the highest heritability is surprising. FALCONER (1955, 1960b) obtained estimates of 0.15 and 0.12 for the heritability of number born where the females were entirely progeny from first litters. In the present case the female parents were

TABLE 11

*Estimates of heritability and maternal effects contribution**

	Trait				
	Y_1	Y_2	Y_3	Y_4	Y_5
Heritability (percent)	20	8	16	16	12
Maternal effects (percent)	0	2	10	9	2

* Negative estimates considered zero.

from both first and second litters. FALCONER (1960b) also obtained a realized heritability of 0.145 from selection for increased litter size.

The components of variance involving series have a bearing on the type of estimation procedure which is appropriate for the various traits. The estimates of σ_{mf}^2 from both Design I and Design II were biased by the interaction components σ_{smf}^2 and σ_{sf}^2 . Design III was proposed because of the uncertainty regarding the magnitude of the latter two components.

The interpretation of σ_{smf}^2 and σ_{sf}^2 is uncertain because of the dual nature of the effects s_i and f_k . Series effects reflect the extent to which factors in the environment were not standard from one series of matings to another. These effects may be of two types: extrinsic environmental conditions in the colony and variations in maternal environment with age of the mother. The latter contribution is dependent on the magnitude of maternal effects variance and rate of maternal maturity, while the former can be important even when environmental control is conscientiously practiced. Since the contribution of the mother may be of two types variability from $(sf)_{ik}$ may arise from genotype-environmental interaction, interactions of maternal effects and some extrinsic environmental factor, or from differences among females in the change in maternal performance from one age to another. The latter situation is known to exist for lactational expression in dairy cattle.

The effects reflected by σ_{smf}^2 must be classified as genotype-environmental interactions since the male parent contributes only genetic material to the offspring.

One of the most anomalous features of the results is the large value obtained for the combined estimate of $(\sigma_{smf}^2 + \sigma_{sf}^2)$ for the growth traits. The values 29 percent, 26 percent and 27 percent for weaning weight, six-week weight, and post-weaning gain seem rather unreasonable, even in light of BRUMBY's report (1960) and some *a priori* expectation of individual differences among females in lactation change with age. Much smaller values were obtained for the litter traits, but these are still large enough to interfere with estimates of σ_{mf}^2 which might be obtained with Diallel Design I or II.

SUMMARY

Three designs for the measurement of the interaction variance of parental genotypes were discussed. The first two are biased by the effects of time trends and differences in maternal environment with age. The third design gives an

estimate which is unbiased, but subject to a large sampling error. In addition, the design is difficult to execute and consequently difficult to analyze.

The choice of an experimental design must be based on knowledge of the contributing sources of variability. The data indicated that traits which (1) have large maternal components, (2) are markedly influenced by maturity of the mother, and (3) exhibit interaction of genotype of the young with maternal environment of the mother, should not be studied using Diallel Design I or II.

For traits meeting the above conditions, two alternatives to the use of Design III are available: (1) use of crosses among inbred lines, or (2) use of artificial insemination with mixed semen to produce progeny of two mates within the same litter. The former alternative may be prohibitively expensive if one wishes to study a particular population. Whether the second method will yield an estimate with smaller standard error for a given expenditure of resources is unknown; in addition it is possible only for multiparous species.

Estimates of σ_{mf}^2 by Design III were obtained for growth and maternal traits of a random mating population of *Mus musculus*. Two replicates provided data for number of mice at birth and the 12-day weight of a litter of six mice for 1,161 and 986 litters respectively. Individual weaning weights (three weeks), six-week weights, and gain from weaning to six weeks were obtained on 2,879 mice. The only trait for which evidence of nonadditive hereditary variance was found was the number of mice born in a litter. An estimate representing 28 percent of the total variance and 58 percent of the total hereditary variance was obtained for this characteristic.

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