QUANTITATIVE GENETICS OF SKELETAL VARIATIONS IN THE MOUSE. II. CROSSES BETWEEN FOUR INBRED STRAINS (C3H, DBA, C57BL, BALB/c)^{1,2}

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IN the mouse, there may be 25, 26, or 27 vertebrae between the cranium and sacrum. Inbred strains differ in the percentages of mice with these three numbers of presacral vertebrae and of asymmetrical combinations between them (GREEN 1941, 1951, 1954; GREEN and RUSSELL 1951).

The purpose of this paper is to record and analyze the results of crosses between four standard inbred strains (including two sublines of two of them) which show the known extremes of variation between inbred strains. The method of analysis is the same as that used by GREEN (1954) and will not be repeated in detail here.

The breeding results suggest a multiple-factor model for differences between the inbred strains. However, the amount of nongenetic variation is so large as to obscure the quantitative effects of the genes in segregating generations.

STRAINS AND CROSSES

The four strains used in the breeding experiments varied from zero percent to 92 percent of mice with 25 presacral vertebrae. All strains had some mice with 26 presacral vertebrae, but the percentage varied from three to 90. In one strain, 33 percent of the mice had 27 presacral vertebrae. The percentages of each type in each strain are shown in Table 1. The symbol A_1 stands for asymmetrical combinations of 25 and 26, and A_2 for 26 and 27 vertebrae. In the "asymmetrical" mice, the sacrum is attached to a given vertebra on one side and to the next vertebrae on the other side.

The origins, known genotypes, and other information about the strains are:

1. C3H/BiGn, $AA\ BB\ CC\ DD$, wild type. The sample of 266 mice were from F_{72} to F_{81} . Twenty mice used for crossing with C57BL/10JGn (cross 2R) were from F_{74} and F_{75} . All mice were descended from a single pair in F_{71} , obtained from DR. J. J. BITTNER of the University of Minnesota in April 1950.

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² This paper is dedicated to PROFESSOR L. C. DUNN, with respect and affection, on the occasion of his retirement as Professor of Zoology at Columbia University.

TABLE 1

Percentages of skeletal types in four inbred strains of mice.
 $A_1 = 25/26$ or $26/25$, $A_2 = 26/27$ or $27/26$ presacral vertebrae

Strain	Number of presacral vertebrae					Total
	25	A_1	26	A_2	27	
C3H/BiGn	91.7	5.7	2.6	...	...	266
C3HfB/BiGn	87.2	4.3	8.5	...	...	282*
DBA/1JGn	91.1	4.9	4.0	...	...	405†
DBA/2LwGn	82.7	6.3	11.0	...	...	254*
C57BL/10JGn	3.6	6.6	89.8	...	...	619*
BALB/cJGn	...	0.2	46.4	20.8	32.6	659*

* Includes mice in Table 1 of GREEN 1954.

† Same mice as in Table 1 of GREEN and GREEN 1959.

2. C3HfB/BiGn, *AA BB CC DD*. The sample of 282 mice was from F_{69} to F_{84} in two groups, one from a single pair in F_{68} in a line which had been fostered on C57BL 26 generations earlier, the other from a single pair in F_{71} in a line which had been fostered on C57BL 29 generations earlier. The single pairs in F_{68} and F_{71} were obtained from DR. J. J. BITTNER in April 1950. The 30 mice used in cross 2A with C57BL/10JGn were all from F_{78} to F_{84} , with most recent common ancestors in F_{74} of the line obtained at F_{71} from BITTNER. The 36 mice in cross 6 with BALB/cJGn were from F_{77} to F_{84} with most recent common ancestors in F_{72} of the line obtained at F_{71} from BITTNER. Finally, 24 mice used in cross 8 with DBA/2LwGn were from F_{80} to F_{83} , with common ancestors in F_{74} of the line obtained at F_{71} from BITTNER.

3. DBA/1JGn, *aa bb CC dd*, nonagouti brown dilute. The 405 mice in this sample were from F_{33} to F_{43} in a line started at F_{33} with a single pair obtained from DR. ELIZABETH FEKETE at the Jackson Memorial Laboratory in April 1950. The 35 mice used in cross 5 with C57BL/10JGn were in F_{38} to F_{42} , with most recent common ancestors in F_{36} .

4. DBA/2LwGn, *aa bb CC dd*. The 254 mice in this sample were from F_{34} to F_{44} in a line descended from a single pair in F_{29} obtained from DR. L. W. LAW of the National Cancer Institute in May 1948. The 39 mice used in cross 4 with BALB/cGn were from F_{38} to F_{42} with common ancestors in F_{36} . The 26 mice used in cross 8 with C3HfB/BiGn were from F_{39} to F_{44} with common ancestors in F_{36} .

5. C57BL/10JGn, *aa BB CC DD*, nonagouti. The sample of 619 mice of this strain was from F_{39} to F_{47} , descended from a single pair in F_{35} (?) obtained from the Jackson Memorial Laboratory in December 1948. The 20 mice used in cross 2R with C3H/BiGn were from F_{41} and F_{42} with common ancestors in F_{40} . The 34 mice used in cross 2A with C3HfB/BiGn were from F_{44} to F_{47} with common ancestors in F_{40} . Finally, 36 mice used in cross 5 with DBA/1JGn were from F_{43} to F_{47} with common ancestors in F_{40} .

6. BALB/cJGn, *AA bb cc DD*, albino carrying brown. The sample of 659 mice was from F_{42} to F_{52} with common ancestors in F_{41} . This stock was obtained

originally from DR. G. D. SNELL of the Jackson Memorial Laboratory in September 1938. My F_1 were progeny of SNELL's F_{36} . The 44 mice used in cross 4 with DBA/2LwGn were from F_{44} to F_{52} , with common ancestors in F_{41} (in my numbering of generations). The 38 mice used in cross 6 with C3HfB/BiGn were from F_{44} to F_{48} with common ancestors in F_{41} .

All mice were dissected and cleared and the skeletons stained by the method of MARGARET C. GREEN (1952). The vertebrae were routinely counted after placing the stained skeleton on a glass plate with diffuse light underneath.

The crosses were designated as follows:

Cross 8	C3HfB $\times$ DBA/2
Cross 5	DBA/1 $\times$ C57BL/10
Cross 4	DBA/2 $\times$ BALB/c
Cross 2R	C3H $\times$ C57BL/10
Cross 2A	C3HfB $\times$ C57BL/10
Cross 6	C3HfB $\times$ BALB/c

The general plan of the breeding experiments was to cross any two strains, P_1 and P_2 , reciprocally, to produce F_1 hybrids, to intercross the F_1 hybrids to produce the F_2 generation, and to backcross F_1 females to males of the parental strains to produce first backcross generations B_1 and B_2 . It was not feasible to pursue this general plan for each cross. The generations actually produced are shown in Tables 3 to 8.

RESULTS

The two sublines of C3H, while similar in the relative frequencies of the different numbers of presacral vertebrae, give such different results in crosses that they cannot be used interchangeably. The same is true for the two sublines of DBA (Table 1). The distributions of the present samples of C3H, C57BL, and BALB/c are all different from the distributions reported in earlier papers (GREEN 1941, 1951; GREEN and RUSSELL 1951). Despite this, there are clear differences between the strains as judged from these samples. The C3H and DBA strains all tend to have high percentages of mice with 25 presacral vertebrae, quite low percentage with 26 presacral vertebrae, and quite low percentages of asymmetricals, A_1 . The C57BL strain is the reverse. It has low percentages of 25 and A_1 , and a high percentage of 26. In the BALB/c strain, about 50 percent have 26 presacral vertebrae, about 30 percent have 27, and about 20 percent are asymmetricals, A_2 .

How much of the variability in the inbred strains is genetic and how much is nongenetic is difficult to estimate with the present data. The BALB/c is the only one with enough phenotypic variability to permit a satisfactory test of a parent-offspring association. Four different mating types in this strain produced the same distributions of skeletal types within sampling limits, as shown in Table 2.

This result indicates that there is little, if any, genetic variability in the BALB/c strain with respect to the number of presacral vertebrae even though there is considerable phenotypic variability. The other strains also probably

have very little, if any, genetic variability, but the number of phenotypically different mating types is not adequate for a satisfactory test.

The results of the crosses between the strains listed in Table 1 are summarized in Tables 3 to 8. The parental strains of cross 8 (C3HfB and DBA/2, Table 3) are alike, within sampling limits, but the F_1 generation has significantly more mice with higher numbers of presacral vertebrae than either parental strain. This may be another manifestation of the greater vigor of the hybrids. In all other crosses, however, the F_1 generation is intermediate between the parental

TABLE 2

Percentages of skeletal types in four mating types of BALB/cGn

Parental type		Presacral vertebrae of progeny			Total
Dam	Sire	26	A ₂	27	
26	26	42.2	18.8	38.8	175
26	27	50.0	26.3	23.7	38
27	26	52.7	23.0	24.3	148
27	27	43.0	18.6	38.4	86
		46.5	20.8	32.7	447
$\chi^2 = 10.63$		$\chi^2(6;0.05) = 12.59$			

TABLE 3

Percentages of skeletal types in various generations of cross 8, C3HfB/BiGn $\times$ DBA/2LwGn

Generation	Number of presacral vertebrae					Total
	25	A ₁	26	A ₂	27	
P ₁ = C3H	87.2	4.3	8.5	...	...	282
P ₂ = DBA	82.7	6.3	11.0	...	...	254
F ₁	69.9	11.6	18.5	...	...	292
F ₂	72.7	9.7	17.6	...	...	165
B ₁	85.3	7.8	6.9	...	...	116
B ₂	75.5	13.2	11.3	...	...	151

TABLE 4

Percentages of skeletal types in various generations of cross 5, DBA/1JGn $\times$ C57BL/10JGn

Generation	Number of presacral vertebrae					Total
	25	A ₁	26	A ₂	27	
P ₁ = DBA	91.1	4.9	4.0	...	...	405
P ₂ = C57	3.6	6.6	89.8	...	...	619
F ₁	64.8	17.1	18.1	...	...	559
F ₂	45.8	11.8	42.4	...	...	321
B ₁	78.2	8.2	13.6	...	...	243
B ₂	30.8	17.0	52.2	...	...	247

TABLE 5

Percentages of skeletal types in various generations of cross 4, DBA/2LuGn $\times$ BALB/cJGn

Generation	Number of presacral vertebrae					Total
	25	A ₁	26	A ₂	27	
P ₁ = DBA	82.7	6.3	11.0	...	...	254
P ₂ = BALB	...	0.2	46.4	20.8	32.6	659
F ₁	...	0.3	99.3	...	0.4	547
B ₁	32.2	11.9	55.9	...	...	118
B ₂	2.7	...	95.5	0.9	0.9	111

TABLE 6

Percentages of skeletal types in various generations of cross 2R, C3H/BiGn $\times$ C57BL/10JGn

Generation	Number of presacral vertebrae					Total
	25	A ₁	26	A ₂	27	
P ₁ = C3H	91.7	5.7	2.6	...	...	266
P ₂ = C57	3.6	6.6	89.8	...	...	619
F ₁	29.8	17.5	52.7	...	...	400

TABLE 7

Percentages of skeletal types in various generations of cross 2A, C3HfB/BiGn $\times$ C57BL/10JGn

Generation	Number of presacral vertebrae					Total
	25	A ₁	26	A ₂	27	
P ₁ = C3H	87.2	4.3	8.5	...	...	282
P ₂ = C57	3.6	6.6	89.8	...	...	619
F ₁	50.0	18.2	31.8	...	...	532
F ₂	43.2	10.7	46.1	...	...	206
B ₁	66.3	12.2	21.5	...	...	205
B ₂	24.7	14.5	60.8	...	...	194

TABLE 8

Percentages of skeletal types in various generations of cross 6, C3HfB/BiGn $\times$ BALB/cJGn

Generation	Number of presacral vertebrae					Total
	25	A ₁	26	A ₂	27	
P ₁ = C3H	87.2	4.3	8.5	...	...	282
P ₂ = BALB	...	0.2	46.4	20.8	32.6	659
F ₁	0.4	...	99.4	0.2	...	470
B ₁	20.6	15.8	63.6	...	...	165
B ₂	1.2	...	95.2	2.4	1.2	165

strains. The distributions of the F_2 , B_1 , and B_2 generations in all crosses where these generations were produced suggests a multiple-factor model of quantitative inheritance, probably with relatively small numbers of pairs of genes distinguishing the parental strains, but with a relatively large amount of nongenetic variation. It is obvious that no model based upon the frequency concepts of mendelian genetics can account for the results.

A model of many pairs of genetic factors with thresholds separating the graded skeletal types of mice appeared to fit the data of earlier experiments (GREEN 1954) somewhat better than one-pair and two-pair genetic models. The same appears to be true for the results of the present experiments.

Under this model, the parental strains, P_1 and P_2 , of any cross are supposed to differ by n pairs of alleles affecting the skeletal type, the "minus" alleles being concentrated in P_1 , the "plus" alleles in P_2 . The variances of P_1 , P_2 , and F_1 are assumed to be equal and genetic causes of variability within these generations are regarded as negligible. The "plus" alleles are assumed to have equal and additive effects on the phenotype. There may be any degree of dominance (allelic interaction). It is further assumed that the loci are not linked and that there is no epistasis (nonallelic interaction). The nongenetic variance, the additive genetic variance, the average dominance, and the minimum number of pairs of alleles may be estimated from the data.

A scale must be chosen which, as nearly as possible, equates the parental and F_1 variances and satisfies certain linear relationships between the means of various generations. The choice of a scale for variation in the number of presacral vertebrae presents more than the usual difficulties because of the small number of observable phenotypes, the uncertainty that unit changes in the number of vertebrae, from 25 to 26 or from 26 to 27, have the same genetic meaning, and the existence of asymmetrical types.

We assume, under the additive genetic model, that there is a continuous scale of factor combinations which may be marked into five intervals (25, A_1 , 26, A_2 , and 27 psv) by four thresholds T , U , V , and W . The thresholds were located on the scale so as to make the variances of the inbred strains and the F_1 generations as alike as possible. The means and variances of each parental and F_1 generation were first located on a standard normal scale, using the transformation of percentages into deviates first used by WRIGHT (1934). Next the means and variances of these generations were rescaled on a "threshold unit scale," denoted by x , such that $x_U = 0$ and $x_W - x_V = 1$. The data led to the further choice of $x_T = -0.84$ and $x_V = 8.15$. Finally the means and variances of the available segregating generations were estimated using the threshold unit scale defined by the nonsegregating generations. The means and standard deviations thus computed for all generations are shown in Table 9.

The variance (3.58^2) of strain C3HeB appeared to be much larger than the variances of the other strains and F_1 hybrids. The variance (2.95^2) of DBA/2 was next in size. The smallest variance (1.57^2) was in the F_1 of cross 5. Rather than try more complicated transformations of scale at this point, it seemed better to accept these variances and look at other tests of the adequacy of the scale. The

TABLE 9

Computed means and standard deviations and expected means of all generations in six crosses on a threshold unit scale. $x_U = 0$, $x_W - x_V = 1$, $x_V = 8.15$

Generation	Cross					
	8	5	4	2R	2A	6
Computed means, $\bar{x}$						
P ₁	-2.56	-3.28	-2.29	-3.61	-2.56	-2.56
P ₂	-2.29	2.39	8.31	2.39	2.39	8.31
F ₁	-1.67	-1.70	3.15	0.13	-0.88	2.81
F ₂	-1.74	-0.36	...	...	-0.18	...
B ₁	-2.77	-2.05	0.28	...	-1.48	0.65
B ₂	-2.26	0.10	4.24	...	0.51	4.80
Computed standard deviations, s						
P ₁	3.58	2.05	2.95	1.52	3.58	3.58
P ₂	2.95	1.60	1.87	1.60	1.60	1.87
F ₁	2.23	1.57	(2.22)*	1.81	1.77	(2.50)*
F ₂	2.56	2.81	...	...	3.12	...
B ₁	1.94	2.61	2.68	...	2.27	1.78
B ₂	1.60	1.88	3.72	...	2.05	2.17
Expected means, $E(\bar{x})$						
F ₂ (E ₁)	-2.52	-0.97	2.26	...	-0.48	2.73
F ₂ (E ₂)	-2.05	-1.07	3.08	...	-0.48	2.84
B ₁	-2.12	-2.49	0.43	...	-1.72	0.13
B ₂	-1.98	0.34	5.73	...	0.75	5.56

* From weighted standard deviations of P₁ and P₂.

variances of the segregating generations should be larger than the variances of the nonsegregating generations, except for sampling fluctuations, provided there are genetic as well as nongenetic causes of variation. This was the case in general except in cross 8 in which the parental strains were themselves nearly alike in phenotype.

The linear relationship between the means of the segregating and nonsegregating generations, under an additive genetic model, are:

$$\begin{aligned}
 E_1(\bar{x}_{F2}) &= (m_{B1} + m_{B2})/2 \\
 E_2(\bar{x}_{F2}) &= (m_{P1} + 2m_{F1} + m_{P2})/4 \\
 E(\bar{x}_{B1}) &= (m_{P1} + m_{F1})/2 \\
 E(\bar{x}_{B2}) &= (m_{F1} + m_{P2})/2
 \end{aligned}$$

where m_{P1} , m_{P2} , ... denote the true means of the P₁, P₂, ... generations and $E(\bar{x}_{F2})$, ... denotes the expected means of F₂, ... The first and second equations test the location of the F₂ mean; the third and fourth test the locations of the B₁ and B₂ means. The expected means are also shown in Table 9.

The agreement between the observed and expected means may be tested by forming four statistics D_i , which have expected values of zero if the agreement is perfect (MATHER 1949). The standard errors, s_i , of the D_i 's may be computed

from the variances of the means of the various generations. Four test statistics useful with the present experiments are:

$$\begin{aligned} D_1 &= 2\bar{x}_{F_2} - \bar{x}_{B_1} - \bar{x}_{B_2}, \\ D_2 &= 2\bar{x}_{B_1} - \bar{x}_{P_1} - \bar{x}_{F_1}, \\ D_3 &= 2\bar{x}_{B_2} - \bar{x}_{F_1} - \bar{x}_{P_2}, \\ D_4 &= 4\bar{x}_{F_2} - \bar{x}_{P_1} - 2\bar{x}_{F_1} - \bar{x}_{P_2}; \end{aligned}$$

and their variances are:

$$\begin{aligned} s_1^2 &= 4s_{F_2}^2 + s_{B_1}^2 + s_{B_2}^2, \\ s_2^2 &= 4s_{B_1}^2 + s_{P_1}^2 + s_{F_1}^2, \\ s_3^2 &= 4s_{B_2}^2 + s_{F_1}^2 + s_{P_2}^2, \\ s_4^2 &= 16s_{F_2}^2 + s_{P_1}^2 + 4s_{F_1}^2 + s_{P_2}^2, \end{aligned}$$

where, to avoid a more cumbersome notation, $s_{P_1}^2, \dots, s_{B_2}^2$ stand for the variances of the *means* of generations $P_1, P_2, \dots, B_2$. These variances were computed by use of a formula derived in subsection of Computation of Variance.

The four scaling tests D_i were computable in only three of the experiments, crosses 8, 5, and 2A. In cross 2R, too few generations were produced. In crosses 4 and 6, F_2 generations were not produced and the uncertainty of the location of the F_1 and B_2 means vitiates any scaling tests. The results of the feasible scaling tests are shown in Table 10. The tests are, with one exception, all non-

TABLE 10
Scaling tests for crosses 8, 5, and 2A

Scale test	Cross		
	8	5	2A
$D_1 \pm s_1$	1.55 ± 1.13	1.23 ± 0.63	0.60 ± 0.37
$D_2 \pm s_2$	-1.30 ± 1.60	0.88 ± 1.05	0.49 ± 0.89
$D_3 \pm s_3$	-0.56 ± 0.75	-0.48 ± 0.40	-0.48 ± 0.50
$D_4 \pm s_4$	1.24 ± 1.11	2.86 ± 0.90	1.21 ± 0.88

significant, giving thereby support to the assumptions of the multiple factor model. The exceptional test, D_4 for cross 5, shows that the F_2 mean is larger than expected on the basis of the parental and F_1 means. The F_2 mean should lie midway between the F_1 mean and the midparent, assuming neither linkage nor nonallelic interactions. The observed F_2 mean, -0.36 , is 0.71 of a threshold unit above its expected location of -1.07 .

The square of the difference between the parental means and the additive genetic variance may be used to estimate the minimal number of pairs of genes which distinguish any two strains. The estimates for the crosses for which there were adequate data were: cross 8, zero pairs; cross 5, two pairs; cross 4, two pairs; cross 2A, two pairs; and cross 6, six pairs. These estimates are internally consistent, except for cross 4 which appears to be too low, probably because the

estimate of the genetic variance in this cross was too high, relative to the difference between the means. In summary, C3HfB and DBA/2 are apparently not genetically different, but they each differ from C57BL/10 by two pairs of genes. C57BL/10 differs from BALB/c by three or four pairs of genes at least (GREEN 1951) and C3HfB differs from BALB/c by six pairs at least. One would expect, if these estimates are dependable, to find that DBA/2 and BALB/c, which differ so much in phenotypic distributions, are also different by at least six pairs of genes, but the estimate from cross 4 is much lower.

Computations of variance: The asymptotic variance of the mean of a two-threshold quantitative character may be found by applying the general methods of calculating asymptotic variances (CRAMÉR 1946; WILKS 1962) to the specific case:

Let t be $N(\mu, \sigma)$, let t_1 and t_2 ($t_2 > t_1$) be scale points or thresholds, and let

$$\pi_1 = \Phi\left(\frac{t_1 - \mu}{\sigma}\right), \quad \pi_2 = \Phi\left(\frac{t_2 - \mu}{\sigma}\right),$$

where $\Phi(y)$ is the normal probability function. Thence

$$t_1 = \mu + \sigma\Phi^{-1}(\pi_1), \quad t_2 = \mu + \sigma\Phi^{-1}(\pi_2),$$

where $\Phi^{-1}(w)$ is the normal inverse probability function, i.e., w is the probability whose deviate is $\Phi^{-1}(w)$. Further let

$$z_1 = \phi\left(\frac{t_1 - \mu}{\sigma}\right), \quad z_2 = \phi\left(\frac{t_2 - \mu}{\sigma}\right),$$

where $\phi(y)$ is the normal density function.

If $c = t_2 - t_1$ is taken as a unit of scale and if t_1 is taken as a new origin, then a transformed scale point x is

$$x = (t - t_1)/(t_2 - t_1) \equiv (t - t_1)/c,$$

with mean

$$m = (\mu - t_1)/(t_2 - t_1) \equiv (\mu - t_1)/c$$

and standard deviation

$$s = \sigma/c.$$

Now

$$\begin{aligned} c &= t_2 - t_1 \\ &= (\mu + \sigma\Phi^{-1}(\pi_2)) - (\mu + \sigma\Phi^{-1}(\pi_1)) \\ &= \sigma(\Phi^{-1}(\pi_2) - \Phi^{-1}(\pi_1)), \end{aligned}$$

and

$$\begin{aligned} \mu - t_1 &= \mu - (\mu + \sigma\Phi^{-1}(\pi_1)) \\ &= -\sigma\Phi^{-1}(\pi_1). \end{aligned}$$

Thus

$$(1) \dots m = -\Phi^{-1}(\pi_1)/(\Phi^{-1}(\pi_2) - \Phi^{-1}(\pi_1)).$$

If the observations, in a sample size n , are frequencies in three categories (below t_1 , between t_1 and t_2 , above t_2), we may define cumulative frequencies as

f_1 , all observations below t_1 , and
 f_2 , all observations below t_2 , including those below t_1 .

Then

$p_1 = f_1/n$ is a maximum likelihood estimate of π_1 , and
 $p_2 = f_2/n$ is a maximum likelihood estimate of π_2 .

Thus the MLE of m ($\hat{m}$) from such data is

$$(2) \dots \hat{m} = -\Phi^{-1}(p_1)/(\Phi^{-1}(p_2) - \Phi^{-1}(p_1)).$$

The asymptotic variance of $\hat{m}$ (σ_m^2) may be found by a Taylor series expansion:

$$\begin{aligned} dm &= \frac{\partial m}{\partial t_1} dt_1 + \frac{\partial m}{\partial t_2} dt_2 \\ &= \frac{t_2}{c^2} dt_1 + \frac{t_1}{c^2} dt_2. \end{aligned}$$

Noting that

$$d\pi_i = z_i dt_i, (i = 1, 2)$$

we see that

$$dm = -\frac{t_2}{c^2 z_1} d\pi_1 + \frac{t_1}{c^2 z_2} d\pi_2.$$

Squaring and expanding each side and substituting estimates p_i for probabilities π_i , gives the asymptotic variance of the mean

$$(3) \dots \sigma_m^2 = \frac{t_2^2}{c^4 z_1^2} \sigma_{p_1}^2 - \frac{2t_1 t_2}{c^4 z_1 z_2} \sigma_{p_1 p_2} + \frac{t_1^2}{c^4 z_2^2} \sigma_{p_2}^2.$$

The variances and covariances of the p_i 's are

$$\begin{aligned} \sigma_{p_i}^2 &= p_i(1 - p_i)/n \quad (i = 1, 2) \\ \sigma_{p_1 p_2} &= p_1(1 - p_2)/n. \end{aligned}$$

Substituting

$$(4) \dots \sigma_m^2 = \{t_2^2 p_1(1 - p_1)/z_1^2 - 2t_1 t_2 p_1(1 - p_2)/z_1 z_2 + t_1^2 p_2(1 - p_2)/z_2^2\}/c^4 n.$$

DISCUSSION

From the results of the experiments on crossbreeding of four inbred strains of mice reported in this paper and of three strains reported in GREEN (1954), we may infer that, with respect to numbers of presacral vertebrae:

1. The differences from strain to strain are genetic.
2. The variation within highly inbred strains is probably almost exclusively nongenetic.
3. The phenotypic distribution of a group of mice is not, by itself, a good indicator of its genetic composition. Some segregating generations are more uniform, some less uniform in type than the F_1 and parental generations.
4. The underlying distribution which represents the combinations of genetic and nongenetic factors affecting the number of presacral vertebrae may be regarded as normal or nearly normal in form, even though the phenotypes are expressed in, at most, seven categories.

5. Selection for a higher or lower number of presacral vertebrae would probably be effective if one starts with a genetically heterogeneous population, such as double cross hybrids, but the selection limit may not lie outside the range of distributions of existing inbred strains.

6. Experimental changes in the environment of developing mice, such as chemical treatments of the mother or inanition, may be expected to change the percentages of the various numbers of presacral vertebrae, but not to bring about an abrupt conversion of the treated mice to a new number of presacral vertebrae.

SUMMARY

Four inbred strains of mice (including two sublines of two strains) which differ in characteristic numbers of presacral vertebrae were crossed in all possible ways and propagated into segregating generations. The strains were C3H/BiGn and C3HfB/BiGn, DBA/1JGn and DBA/2LwGn, C57BL/10JGn, and BALB/cJGn. The breeding results suggest a multiple-factor genetic model for the differences between the strains. The large amount of phenotypic variability within the inbred strains is probably almost all nongenetic. In the segregating generations, this nongenetic variability obscures the genotypic classes, even though the number of pairs of factors which distinguish the strains is apparently not large.

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