THE SEPARATION OF EPISTATIC FROM ADDITIVE AND DOMINANCE VARIATION IN GENERATION MEANS

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1. INTRODUCTION

MATHER (1949) introduced tests of generation means for epistasis which were elaborated by Cavalli (1952), Anderson and Kempthorne (1954), Jinks (1956) and Hayman (1957). Models of certain epistatic systems were described by Griffing (1950), Powers (1951) and Horner, Comstock and Robinson (1955). More general models were developed by Anderson and Kempthorne (1954), Hayman (1954*a*) and Hayman and Mather (1955) to describe the genetic variation present in two inbred lines and their descendant families. Anderson and Kempthorne showed in particular that all the information about additive, dominance and digenic epistatic variation available in the means of generations descended from two inbred lines is contained in just six parameters.

Here we describe the estimation from various experiments of six related parameters. We discover whether any useful measures of epistasis exist and investigate the problem of separating additive and dominance effects from epistatic effects.

2. THEORY

If two inbred lines differ by any number of unlinked genes the expectations of their, and some of their descendant, family and generation means may be expressed as

$$\begin{array}{lll}
P & = m + & d - \tfrac{1}{2}h + \quad i - \quad j + \tfrac{1}{4}l \\
P' & = m - & d - \tfrac{1}{2}h + \quad i + \quad j + \tfrac{1}{4}l \\
\mathrm{F}_1 & = m & + \tfrac{1}{2}h \qquad\quad + \tfrac{1}{4}l \\
\mathrm{F}_2 & = m & \\
B & = m + \tfrac{1}{2}d & + \tfrac{1}{4}i \\
B' & = m - \tfrac{1}{2}d & + \tfrac{1}{4}i \\
\mathrm{F}_3 & = m & - \tfrac{1}{4}h \qquad\quad + \tfrac{1}{16}l \\
BS & = m + \tfrac{1}{2}d - \tfrac{1}{4}h + \tfrac{1}{4}i - \tfrac{1}{4}j + \tfrac{1}{16}l \\
BS' & = m - \tfrac{1}{2}d - \tfrac{1}{4}h + \tfrac{1}{4}i + \tfrac{1}{4}j + \tfrac{1}{16}l \\
\mathrm{F}_4 & = m & - \tfrac{3}{8}h \qquad\quad + \tfrac{9}{64}l \\
\textit{i.e.} \quad \text{mean} & = m + \alpha d + \beta h + \alpha^2 i + 2\alpha\beta j + \beta^2 l & \qquad (1)
\end{array}$$

P and P' are the means of the two parent families and F_1 is the mean of their progeny. F_2, F_3 and F_4 are the means of generations descending from this cross by selfing. B and B' are the means of the first backcrosses to the parents while BS and BS' are the means of the progeny of selfing these first backcross families.

The genetic parameters d, h, i, j and l are sums of the gene parameters of Hayman and Mather (1955) as follows :—

$$d = \sum_{a} d_a\theta_a$$
$$h = \sum_{a} h_a$$
$$i = \sum_{a<b} i_{ab}\theta_a\theta_b$$
$$j = \tfrac{1}{2}\sum_{a<b} (j_{ab}\theta_a + j_{ba}\theta_b)$$
$$l = \sum_{a<b} l_{ab}$$

m is the F_2 mean. Summation is over all genes a, b, ... by which the two inbred lines differ. The individual additive gene effects d_a, d_b, ... are taken to be positive and the state of association of the genes in the parents is indicated by the parameters θ_a, θ_b, ... which are positive unity when P contains the positive homozygote of the corresponding gene and negative unity when P' contains the positive homozygote. Thus d measures pooled additive effects and h pooled dominance effects while the epistatic i measures pooled interactions between additive effects, j between additive and dominance effects and l between dominance effects, all with due allowance for association. A parameter similar to h has already been used by Hayman (1954*b*) in connection with diallel crosses.

Anderson and Kempthorne's (1954) six parameters are related to ours by

$$K_2 = m$$
$$E = \tfrac{1}{2}h$$
$$F = d - \tfrac{1}{2}h$$
$$G = \tfrac{1}{4}l$$
$$L = j - \tfrac{1}{2}l$$
$$M = i - j + \tfrac{1}{4}l.$$

Their E and G measure dominance and interactions between dominance effects, like our h and l, but their F, combining additivity and dominance, and their L and M, measuring pooled interactions of the constituents of F, are not so easy to interpret.

Another difference between these two sets of parameters should be explained. Those of Anderson and Kempthorne (1954) explicitly contain interactions between genes by which the parents differ and genes which are identical in the parents, whereas we have not mentioned these interactions. When, as in our case, one cross and its descendants are under consideration such epistasis may be incorporated in m, d and h and ignored as long as attention is confined to genetic material derived from the two parents. Of course, when several crosses with some parents in common are considered, such epistasis must be accounted for in the model because genes for which one pair of parents are identical may have alleles in other parents.

The parameters are fitted by the method of least weighted squares as outlined by Cavalli (1952). The necessity for different weights has a variety of causes. Most important is the reduction in the expected error of the means of later generations occasioned by the great numbers of individuals in these generations. As well as this statistical effect is the *generation effect* noted by Hayman (1957) in maize and cotton. This could be due to differences between heterozygous and homozygous generations or between segregating and genetically homogeneous generations. Stability may also be under genetic control (Jinks and Mather, 1955) and so vary from family to family. Thus each mean has its own error variance E_P, $E_{P'}$, E_{F_1}, etc., obtained from duplicates in the experiment. For example, if V_P is the variance between the n duplicate plots of one parent then $E_P = V_P/n$. We assume that n is large enough for these variances to be assumed reasonably constant. Further, no correlations between means are supposed to arise from the experimental layout.

The first step in the examination of the means is to fit m, d and h and to test for goodness of fit. If the χ^2 is significant m, d, h, i, j and l are fitted and tested. Let the estimates in the first step be $\hat{m}^*$, $\hat{d}^*$ and $\hat{h}^*$ and those in the second step $\hat{m}$, $\hat{d}$, $\hat{h}$, $\hat{\imath}$, $\hat{\jmath}$ and $\hat{l}$.

When epistasis is absent $\hat{m}^*$, $\hat{d}^*$ and $\hat{h}^*$ measure a constant, additivity and dominance. When epistasis is present and the data fit the six-parameter model $\hat{m}$, $\hat{d}$, $\hat{h}$, $\hat{\imath}$, $\hat{\jmath}$ and $\hat{l}$ measure a constant, additivity, dominance and the three kinds of epistasis. In these circumstances the deviations of the observed generation means from their expectations on the three-parameter model are epistatic in nature and reveal just what kinds of epistasis influence any given mean.

When epistasis occurs it would be convenient to be able to derive *epistasis-free* expectations of the generation means or, in other words, to discover what these means would have been if the genes had not interacted interallelically. We use expectations based on $\hat{m}^*$, $\hat{d}^*$ and $\hat{h}^*$, although these contain an epistatic element since m, d and h are not orthogonal to i, j and l in the equations of expectation. A better approach might seem to be to use the estimates of m, d and h from the six-parameter model to supply the expectations. Unfortunately such expectations are also not free of epistasis and we must delve in to the definitions of m, d and h in the presence of epistasis to understand why this should be so. Readers interested in the more practical side of this work should pass straight on to the experimental results.

The difficulty lies in a fundamental difference between genetic and statistical experiments. In a two-factor experiment, such as a nitrogen and phosphorus fertiliser trial with each fertiliser at three levels, the yield at one level of, say, nitrogen is obtained averaged over the three levels of phosphorus. If the fertilisers interact we still measure the mean yield at one level of nitrogen in the same way and we measure the interaction between any particular combination of

nitrogen and phosphorus by the difference between the corresponding observed yield and the average of the mean yields at the particular levels of nitrogen and phosphorus. As far as this experiment is concerned, unique measures of the effects of each fertiliser separately can be obtained whether the fertilisers interact or not. If now the experiment is repeated with the nitrogen at the same three levels but with the phosphorus at three different levels the yield at each level of nitrogen can still be obtained but, if the fertilisers interact, these yields may bear no relation to the yields at each nitrogen level in the first experiment. In other words, the effects of one factor cannot be compared between the two experiments because the other factor has altered. Of course, this often does not matter because each experiment may be sufficient in itself for the time and place at which it is performed.

The analogous genetical factors are genes, each with three levels, AA, Aa and aa. In a two-gene system the additive effect d_a of gene A may be measured by either $\frac{1}{2}(AABB-aaBB)$, $\frac{1}{2}(AABb-aaBb)$ or $\frac{1}{2}(AAbb-aabb)$ or by any average of these three quantities, and dominance h_a of gene A is measured by $AaBB-\frac{1}{2}(AABB+aaBB)$, $AaBb-\frac{1}{2}(AABb+aaBb)$ or $Aabb-\frac{1}{2}(AAbb+aabb)$ or by any average of these quantities. In a particular population the quantities would be averaged in proportion to the frequencies of the levels of the genetic factor B. In an F_2 family, for example, d_a would be an average of the three corresponding quantities above with frequencies $\frac{1}{4}$, $\frac{1}{2}$ and $\frac{1}{4}$ respectively. This one population is the analogue of one statistical experiment above. In an F_3 population the proportions would be $\frac{3}{8}$, $\frac{1}{4}$ and $\frac{3}{8}$ while for some purposes proportions $\frac{1}{2}$, o and $\frac{1}{2}$ are convenient. Each of these populations corresponds in our analogy to a single statistical experiment although the differences between our populations are ones of weight, and not of level, of the factors. If the two genes do not interact all these definitions of d_a and h_a are equivalent and d_a and h_a are defined uniquely but when digenic epistasis occurs the definitions of d_a and h_a in each population are different. Here lies the crux of the matter. One of our genetical experiments contains several populations, each analogous to one of a set of not easily comparable statistical experiments. Further, since we do not make comparisons within our populations, all our comparisons *must* be between populations in each of which our parameters should have different definitions.

Actually the situation is not as hopeless as it might seem, for the fact that the differences between our populations are differences in the proportions and not in the levels of the genetical factors enables us to relate the parameters in the various populations. As a standard it is convenient to define d_a, h_a, i_{ab}, j_{ab} and l_{ab} against an F_2 *background population* at the other loci controlling the character in question. These are the parameters we have introduced above and, with the exception of the constant term, are the parameters of Hayman and

Mather (1955). If $\bar{d}_a$, $\bar{h}_a$, $\bar{i}_{ab}$, $\bar{j}_{ab}$ and $\bar{l}_{ab}$ are defined against a background population with proportions (p, q, r) at the other loci then Hayman (1954*a*) has shown that

$$\begin{aligned}
\bar{m} &= m+\sum_a[(p_a-r_a)d_a+(q_a-\tfrac{1}{2})h_a]+\sum_{a<b}[(p_a-r_a)(p_b-r_b)i_{ab} \\
&\quad +(p_a-r_a)(q_b-\tfrac{1}{2})j_{ab}+(p_b-r_b)(q_a-\tfrac{1}{2})j_{ba}+(q_a-\tfrac{1}{2})(q_b-\tfrac{1}{2})l_{ab}] \\
\bar{d}_a &= d_a+\sum_b[(p_b-r_b)i_{ab}+(q_b-\tfrac{1}{2})j_{ab}] \\
\bar{h}_a &= h_a+\sum_b[(p_b-r_b)j_{ba}+(q_b-\tfrac{1}{2})l_{ab}] \\
\bar{i}_{ab} &= i_{ab} \\
\bar{j}_{ab} &= j_{ab} \\
\bar{l}_{ab} &= l_{ab}
\end{aligned}$$

Here we have assumed that digenic, but no higher order epistasis, may occur. The inverse transformation is obtained by interchanging barred and unbarred parameters and changing the signs of $p-r$ and $q-\frac{1}{2}$. Evidently measures of digenic epistasis can be defined uniquely if higher order epistasis is absent but measures of additivity and dominance defined in one population must be corrected by epistatic terms for use in other populations.

If (p, q, r) describes the proportions in one of the generations in our list above then it may be shown from the above transformation that expectations in terms of parameters defined against a (p, q, r) background population may be written down as follows. Write m alone for the expectation of the mean of the generation in question. Write m together with appropriate terms in d and h for the other generations. Add i, j and l terms in accordance with equation (1).

A useful form is with $(p, q, r) = (\frac{1}{2}, 0, \frac{1}{2})$. Then

$$\begin{aligned}
\bar{m} &= m-\tfrac{1}{2}h+\tfrac{1}{4}l \\
\bar{d} &= d-j \\
\bar{h} &= h-l \\
\bar{i} &= i, \bar{j} = j \text{ and } \bar{l} = l.
\end{aligned}$$

The expectations of the generation means become

$$\begin{aligned}
P &= \bar{m}+\bar{d}+\bar{i} \\
P' &= \bar{m}-\bar{d}+\bar{i} \\
\mathrm{F}_1 &= \bar{m}+\bar{h}+\bar{l} \\
\mathrm{F}_2 &= \bar{m}+\tfrac{1}{2}\bar{h}+\tfrac{1}{4}\bar{l}, \text{ etc.},
\end{aligned}$$

again in accordance with equation (1). This form has the important property that when a generation is selfed the mean of the resulting generation has an expectation derived from its parent's expectation by changing β to $\frac{1}{2}\beta$.

Reverting to our analogy between genetical and statistical experiments we see that we can overcome to some extent the lack of comparability of statistical experiments in our analogous genetical populations and can relate parameters defined in different populations.

Further, our measures of epistasis are actually identical in each population and when we estimate i, j and l from the generation means it does not matter which form the expectations take. However, the estimates of the constant and main effects, m, d and h, vary with the form of the expectations just as the estimates of the effect of each level of nitrogen varied between the two fertiliser trials. It is not possible, therefore, to obtain epistasis-free expectations of the generation means from m, d and h of the six-parameter model.

Here is another way of looking at the matter. In the absence of epistasis $2F_1 - 2F_2$ is a measure of dominance. With digenic epistasis and our standard form of the expectations

$$2F_1 - 2F_2 = h + \tfrac{1}{2}l.$$

In the F_1 form with $(p, q, r) = (0, 1, 0)$

$$2F_1 - 2F_2 = \hat{h} - \tfrac{1}{2}\hat{l}$$

while in the form with $(p, q, r) = (\tfrac{1}{2}, 0, \tfrac{1}{2})$ (and different $\hat{h}$ of course)

$$2F_1 - 2F_2 = \hat{h} + \tfrac{3}{2}\hat{l}.$$

Clearly, if these three forms are corrected for epistasis with the same value of l (or $\hat{l}$), different estimates of dominance must result.

Our approximation to epistasis-free expectations will, therefore, be derived from m, d and h estimated on the assumption of no epistasis —what we have labelled $\hat{m}^*$, $\hat{d}^*$ and $\hat{h}^*$. These expectations are independent of the definition of m, d and h and are unique.

Before considering experimental results it is useful to exhibit this theoretical discussion in matrix form. The equations of expectation become

$$\mathbf{y} = \mathbf{C}\mathbf{x}$$

which may also be written

$$\mathbf{y} = \mathbf{C}_1\mathbf{x}_1 + \mathbf{C}_2\mathbf{x}_2$$

$\mathbf{y}$ is the vector of observed generation means. $\mathbf{C}_1$ is the matrix of coefficients of m, d and h and $\mathbf{C}_2$ is the matrix of coefficients of the epistatic i, j and l. $\mathbf{x}_1$ is the vector of the parameters m, d and h and $\mathbf{x}_2$ is the vector of i, j and l. If $\mathbf{E}$ is the (diagonal) matrix of error variances of the means then the estimates of the parameters are given by

$$\begin{pmatrix}\hat{\mathbf{x}}_1\\ \hat{\mathbf{x}}_2\end{pmatrix} = \hat{\mathbf{x}} = (\mathbf{C}'\mathbf{E}^{-1}\mathbf{C})^{-1}\mathbf{C}'\mathbf{E}^{-1}\mathbf{y} \text{ (where } \mathbf{C}' \text{ is the transpose of } \mathbf{C})$$

and the test of goodness of fit is

$$\chi^2 = \mathbf{y}'\mathbf{E}^{-1}\mathbf{y} - \mathbf{y}'\mathbf{E}^{-1}\mathbf{C}\hat{\mathbf{x}}$$

The error variances and covariances of the estimators are given by the matrix

$$\mathbf{V}(\hat{\mathbf{x}}) = (\mathbf{C}'\mathbf{E}^{-1}\mathbf{C}')^{-1}$$

After transformation to a different background population

$$\mathbf{x}_1 = \mathbf{A}\bar{\mathbf{x}}_1 + \mathbf{B}\bar{\mathbf{x}}_2$$

and

$$\mathbf{x}_2 = \bar{\mathbf{x}}_2$$

$\bar{\mathbf{x}}_1$ and $\bar{\mathbf{x}}_2$ have estimators

$$\hat{\bar{\mathbf{x}}}_1 = \mathbf{A}^{-1}\hat{\mathbf{x}}_1 - \mathbf{A}^{-1}\mathbf{B}\hat{\mathbf{x}}_2$$
$$\hat{\bar{\mathbf{x}}}_2 = \hat{\mathbf{x}}_2$$

so that the estimates of i, j and l are unaffected.

If epistasis is ignored the estimate of $\mathbf{x}_1$ is

$$\hat{\mathbf{x}}_1{}^* = (\mathbf{C}'_1\mathbf{E}^{-1}\mathbf{C}_1)^{-1}\mathbf{C}'_1\mathbf{E}^{-1}\mathbf{y}$$

and the expectations on this three-parameter model are

$$\hat{\mathbf{y}}^* = \mathbf{C}_1\hat{\mathbf{x}}_1{}^*$$

The test of goodness of fit is

$$\chi^2 = \mathbf{y}'\mathbf{E}^{-1}\mathbf{y} - \mathbf{y}'\mathbf{E}^{-1}\mathbf{C}_1\hat{\mathbf{x}}_1{}^*$$

and the variance matrix of the estimators is

$$\mathbf{V}(\hat{\mathbf{x}}_1{}^*) = (\mathbf{C}'_1\mathbf{E}^{-1}\mathbf{C}_1)^{-1}.$$

The expectation of the difference between observation and expectation on this three-parameter model is

$$\mathcal{E}(\mathbf{y} - \hat{\mathbf{y}}^*) = \mathbf{I}_1\mathbf{C}_2\mathbf{x}_2$$

where

$$\mathbf{I}_1 = \mathbf{I} - \mathbf{C}_1\mathbf{V}(\hat{\mathbf{x}}_1{}^*)\mathbf{C}'_1\mathbf{E}^{-1}.$$

Evidently these differences are due entirely to epistasis and their expected variances are given by

$$\mathbf{V}(\mathbf{y} - \hat{\mathbf{y}}^*) = \mathbf{I}_1\mathbf{E}.$$

3. RESULTS

At least six families or generations are necessary for the estimation of the six parameters m, d, h, i, j and l. The most convenient experiment involves P, P', F_1, F_2, B and B' : we give examples of tomato and *Nicotiana rustica* experiments of this kind. Another common type is the selfing experiment containing P, P', F_1, F_2, F_3, etc., which supplies estimates of m, i, h and l but fails to separate d from j : the latter occur only as d-j in P and P'. We give an example carried to F_4 in *Nicotiana rustica*. Finally we describe tomato and wheat experiments involving the first six means, together with *BS* and *BS'* in the tomato experiment, or F_3 in the wheat experiment.

(i) *Experiment* 1: P, P', F_1, F_2, B *and* B'

Powers (1951) describes such an experiment on number of locules per fruit in the two tomato varieties Danmark and Johannisfeuer. He finds that on the logarithmic scale the data satisfy the essential

criterion of normality of the distributions in non-segregating generations. His results on this scale for two years are in the top of table 1A.

The 1939 data fail to fit a non-epistatic model ($\chi^2_3 = 11{\cdot}93$, $P = 0{\cdot}01 - 0{\cdot}001$) so that epistatic parameters should be fitted. The estimates of the parameters are in the lower half of the table, the left set in each case ignoring epistasis and the right (where relevant) allowing for it. Interactions between dominance effects (l) contribute the major portion of the epistasis : this agrees with Powers' (1951, p. 22) conclusion based on a two-gene model. Alongside the observations in the upper half of the table are the differences between them and their expectations on the three-parameter model. The epistasis suppresses the negative dominance in F_1 and enhances it in the F_2 and backcross generations as would duplicate epistasis.

TABLE 1A

Powers' (1951) Danmark × Johannisfeuer tomato cross

Mean number of locules per fruit (logarithmic scale)

	1939		1940
	Observation	Difference	Observation
P	0·7864±0·0048	−0·0033±0·0015	0·7739±0·0080
P'	0·9521±0·0041	0·0021±0·0010	0·9425±0·0052
F_1	0·7764±0·0071	0·0138±0·0042	0·7588±0·0096
F_2	0·8117±0·0083	−0·0029±0·0078	0·8119±0·0133
B	0·7595±0·0071	−0·0134±0·0062	0·7485±0·0073
B'	0·8404±0·0083	−0·0160±0·0076	0·8285±0·0126
	3-parameter model	6-parameter model	3-parameter model
m	0·8146±0·0029	0·8117±0·0083	0·8017±0·0039
d	−0·0835±0·0030	−0·0809±0·0109	−0·0864±0·0044
h	−0·1039±0·0070	−0·1399±0·0505	−0·1070±0·0099
i	.	−0·0470±0·0397	.
j	.	0·0020±0·0113	.
l	.	0·1387±0·0569	.
χ^2_3	11·93		5·85

difference = observed mean − expectation on three-parameter model.

The 1940 data fit a non-epistatic model. However, if estimates of m, d and h together with i, j and l are computed they are closely correlated to those of the previous year and indeed l just reaches significance again. This suggests that the lack of evidence for epistasis in the second year is due to a rise in the error variance rather than to a change in the action of the genes.

Jinks (1956) describes a diallel experiment on eight lines of *Nicotiana rustica* containing parental, F_1, F_2 and backcross generations. Hayman (1957) used the parental, F_1 and F_2 generations of this experiment to classify the individual crosses according to the type of

dominance and epistasis exhibited. We re-analyse the 1952 height data from three of the heterotic crosses to see the effect of the extra backcross information. The means, averaged over blocks and reciprocal crosses, are in table 1B. Family error variances are constant within generations over all crosses in the diallel experiment so that only one set of average standard errors is listed. Two of the crosses do have a parent in common but we ignore this fact because we are only using these experiments for illustration.

TABLE 1B

Jinks' (1956) Nicotiana rustica *crosses*

Mean height in inches

	1×2		3×4		4×5	General difference
	Observation	Difference	Obs.	Diff.	Obs.	
P	33·50±2·02	−1·41±1·06	27·40	−5·18	51·30	$0{\cdot}2210i-0{\cdot}2592j+0{\cdot}1467l$
P'	38·30±2·02	0·74±1·06	51·30	1·86	35·80	$0{\cdot}2201i+0{\cdot}2592j+0{\cdot}1467l$
F_1	51·00±1·43	−0·33±0·77	55·55	−1·66	53·20	$0{\cdot}2201i+0{\cdot}1467l$
F_2	39·58±1·19	−4·20±1·00	52·48	3·37	47·93	$-0{\cdot}2790i-0{\cdot}1033l$
B	49·45±1·71	6·33±1·45	48·85	3·96	51·80	$-0{\cdot}0290i+0{\cdot}3704j-0{\cdot}1033l$
B'	47·70±1·71	3·26±1·45	47·20	−6·13	46·40	$-0{\cdot}0290i-0{\cdot}3704j-0{\cdot}1033l$
	3-parameter model	6-parameter model	3-p. model	6-p. model	3-p. model	
m	43·78±0·65	39·58±1·19	49·11	52·48	48·45	Difference equals observed mean minus expectation on the 3-parameter model
d	−1·32±1·23	1·75±2·41	−8·43	1·65	7·14	
h	15·15±2·02	51·08±7·07	16·20	−1·62	9·65	
i	.	35·98±6·78	.	−17·82	.	
j	.	4·15±2·80	.	13·60	.	
l	.	−56·48±11·49	.	15·52	.	
χ^2_3	30·67		35·24		1·21	

The standard errors of each quantity are the same in every cross.

Since this P, P', F_1, F_2, B and B' experiment with error variances E_P, E_1, E_2 and E_B in the four generations is probably the most important of our experiments we give here the detailed expansion of the previous matrix formulas. When epistasis is absent, or is ignored, the estimates of m, d and h are

$$\begin{aligned}
2E^2\hat{m}^* &= 2E_2E_B(P+P'+2F_1)+(E_P+2E_1)(E_BF_2+E_2(B+B')) \\
(E_P+4E_B)\hat{d}^* &= 2E_B(P-P')+E_P(B-B') \\
E^2\hat{h}^* &= 2E_2E_B(2F_1-P-P')+E_1E_B(2F_2-P-P')+ \\
&\quad 2E_1E_2(B+B'-P-P')+E_PE_B(F_1-F_2)+ \\
&\quad E_PE_2(2F_1-B-B')
\end{aligned}$$

where $2E^2 = (E_P+2E_1)(2E_2+E_B)+8E_2E_B$

These may be tested for significance against

$$\begin{aligned}
2E^2 \text{ var } \hat{m}^* &= E_2E_B(E_P+2E_1) \\
(E_P+4E_B) \text{ var } \hat{d}^* &= 2E_PE_B \\
E^2 \text{ var } \hat{h}^* &= 4E_1E_2E_B+2E_PE_2E_B+2E_PE_1E_B+4E_PE_1E_2
\end{aligned}$$

The test for epistasis is a χ^2 with three degrees of freedom which may be written

$$\{E_B(P+P'+2F_1-4F_2)^2+2E_2(P+P'+2F_1-2B-2B')^2+$$
$$(E_P+2E_1)(2F_2-B-B')^2\}/4E^2+(P-P'-2B+2B')^2/(2E_P+8E_B)$$

The squared terms are linear combinations of the A, B and C used by Mather (1949) to test for epistasis.

When epistasis is present the six parameters provide an exact fit to the generation means and their estimates are

$$\begin{aligned}
\hat{m} &= F_2 \\
\hat{d} &= \tfrac{1}{2}P-\tfrac{1}{2}P' \\
\hat{h} &= -\tfrac{1}{2}P-\tfrac{1}{2}P'+F_1-4F_2+2B+2B' \\
\hat{i} &= -4F_2+2B+2B' \\
\hat{j} &= -\tfrac{1}{2}P+\tfrac{1}{2}P'+B-B' \\
\hat{l} &= P+P'+2F_1+4F_2-4B-4B'
\end{aligned}$$

Since these equations do not involve the error variances they were also used with the previous data of Powers. The expected variances and covariances of the parameters are linear combinations of the error variances. For example,

$$\begin{aligned}
\operatorname{var} j &= \tfrac{1}{2}E_P+2E_B \\
\operatorname{cov}(i, l) &= -16E_2-16E_B
\end{aligned}$$

The first two *Nicotiana rustica* crosses in table 1B exhibit epistasis—i and l types in the first and i and j types in the second. All three show dominance, but not necessarily additive, variation—which is not surprising in experiments selected for heterosis. At the right of the table are the expectations in terms of i, j and l of the differences between observed and expected means. The relative importance of the three kinds of epistasis to these deviations can be seen at a glance.

We can compare these results with Hayman's (1957) results based on parental, F_1 and F_2 data alone. Hayman classified crosses as complementary epistatic, non-epistatic or duplicate epistatic: in a non-epistatic cross the F_2 mean lay midway between the midparent and the F_1 mean, in a complementary cross the F_2 mean was nearer to the midparent and in a duplicate cross nearer to the F_1 mean, the deviations of the F_2 mean from the midway point being proportional to $2i+l$ in our present notation. It is clear from table 1B that 1×2 would be complementary, 3×4 duplicate and 4×5 non-epistatic on this system of classification.

The addition of backcross information reveals a more complicated situation. Whereas in the tomato data in table 1A the backcross deviations followed the F_2 deviations, here the epistatic deviations in the backcrosses are generally opposite to those in the F_2 and there are also differences between the two backcrosses themselves. The simple one-way classification breaks down and a three-way classification in terms of i, j and l is necessary.

It also follows that the relationship between epistasis and heterosis cannot be as simply characterised as in Hayman's (1957) paper. Comparisons between the midparent deviation on the one hand and either the F_1, F_2 or mean backcross deviations on the other hand should reveal the effect of epistasis on apparent dominance, or more correctly on heterosis since all three crosses were selected as heterotic. Now for statistical reasons the difference between observation and expectation for the midparent happens to be the same as the difference for the F_1 in this experiment (see final column of table 1B) so that we must turn to the F_2 and mean backcross for information. The deviations in F_2 are in agreement with Hayman's (1957) classification, *viz.* in 1×2 epistasis depresses the F_2 relative to the midparent, in 3×4 it enhances it while in 4×5 it leaves it unaffected. The deviations in the mean backcross are just opposite in sign to the F_2 deviations in 1×2 and 3×4 and, of course, negligible in 4×5. The evidence from these three crosses supports Hayman's (1957) conclusion that, in *Nicotiana rustica*, heterosis may be enhanced or diminished by epistasis or may occur independently of it.

(ii) *Linkage*

Linkage only affects the epistatic terms in the generation means. While failure to fit the non-epistatic model (m, d and h) is a definite indication of epistasis, failure to fit the digenic epistatic model (m, d, h, i, j and l) may indicate either trigenic epistasis or linkage or both. If p_{ab} is the linkage between genes a and b the estimators of the parameters in the present experiment have expectations

$$\hat{m} = m$$
$$\hat{d} = d$$
$$\hat{h} = h - \sum_{a,b} (1 - 2p_{ab})(i_{ab}\theta_a\theta_b + j_{ab}\theta_a + j_{ba}\theta_b - 2p_{ab}l_{ab})$$
$$\hat{i} = i - \Sigma(1 - 2p_{ab})(i_{ab}\theta_a\theta_b + j_{ab}\theta_b + j_{ba}\theta_b - 2p_{ab}l_{ab})$$
$$\hat{j} = j$$
$$\hat{l} = l + \Sigma(1 - 2p_{ab})(2j_{ab}\theta_a + 2j_{ba}\theta_b - (1 + 2p_{ab})l_{ab})$$

Three of the parameters, m, d and j and the difference h-i are still estimated correctly but h and i, separately, and l are disturbed by epistatic linkage terms. It is not possible to determine the two extra terms which have appeared here by adding later generations because the powers of p are higher, and these two extra terms do not appear, in the expectations of later generation means (Hayman, 1954*a*).

(iii) *Experiment 2: P, P', F_1, F_2, F_3 and F_4*

Three lines of *Nicotiana rustica* (which were also lines 1, 2 and 4 of Jinks' (1956) diallel experiment) were set out as a small diallel in which each cross was selfed up to the F_4 generation. The complete experiment was grown in Birmingham in 1954 and again in 1955.

Table 2 contains the mean heights and standard errors of each family or generation of the cross 1 ×2 and its descendants in the two years.

The expectations of the means may be written

$$P = m + d' - \tfrac{1}{2}h + i + \tfrac{1}{4}l$$
$$P' = m - d' - \tfrac{1}{2}h + i + \tfrac{1}{4}l$$
$$F_n = m - (\tfrac{1}{2} - 2^{-n+1})h + (\tfrac{1}{2} - 2^{-n+1})^2 l \qquad n = 1, 2, 3, 4$$

where $d' = d - j$. Only five parameters can be estimated from this

TABLE 2

Hayman's Nicotiana rustica *selfing experiment*

Mean height in inches

	1954		1955	
	Observation	Difference	Observation	Difference
P	41·42±0·49	0·31±0·14	32·78±0·34	−0·84±0·10
P'	39·30±1·09	1·54±0·69	42·02±0·78	−4·37±0·54
F_1	46·46±0·89	−0·45±0·28	52·18±0·60	−0·84±0·21
F_2	45·72±1·49	2·55±1·42	46·64±0·92	0·13±0·88
F_3	47·73±1·44	6·43±1·40	43·86±0·64	0·60±0·60
F_4	38·36±0·57	−2·00±0·43	43·53±0·35	1·89±0·26
	3-parameter model	5-parameter model	3-parameter model	5-parameter model
m	43·17±0·44	48·25±1·33	46·51±0·28	46·26±0·76
d'	1·68±0·53	1·06±0·60	−6·39±0·37	−4·62±0·43
h	7·48±1·02	12·78±1·50	13·02±0·69	9·36±0·95
i	.	6·81±1·42	.	−5·44±0·90
l	.	−33·27±7·70	.	5·07±4·55
χ^2_3	37·99		68·72	
χ^2_1		14·31		0·54

Difference = observed mean − expectation on the 3-parameter model.

experiment : four, m, h, i and l, are as before but d', measuring the spread of the parents, is a compound of additive effects and interaction between additive and dominance effects.

A χ^2 with three degrees of freedom tests for epistasis and a χ^2 with one degree of freedom for linkage or trigenic epistasis. In 1955 digenic epistasis is present and fig. 1 shows the relations between the various expectations. The full line joins the midparent and the other successive generation means. Heterosis is marked here. The broken line joins expectations derived from the best fitting simple m, d and h model. The dotted line joins expectations on the complete five-parameter model. The epistatic terms account well for the failure of the generation means to fall with inbreeding as they should on a simple dominance model. Epistasis is responsible for some of the heterosis because the excess of the F_1 over the midparent is significantly less for the three-parameter expectations than for the observed means.

In 1954 even the five-parameter model fails to account for the variation between the generation means. It appears that epistasis is suppressing heterosis in the F_1 but a more comprehensive model might reveal otherwise.

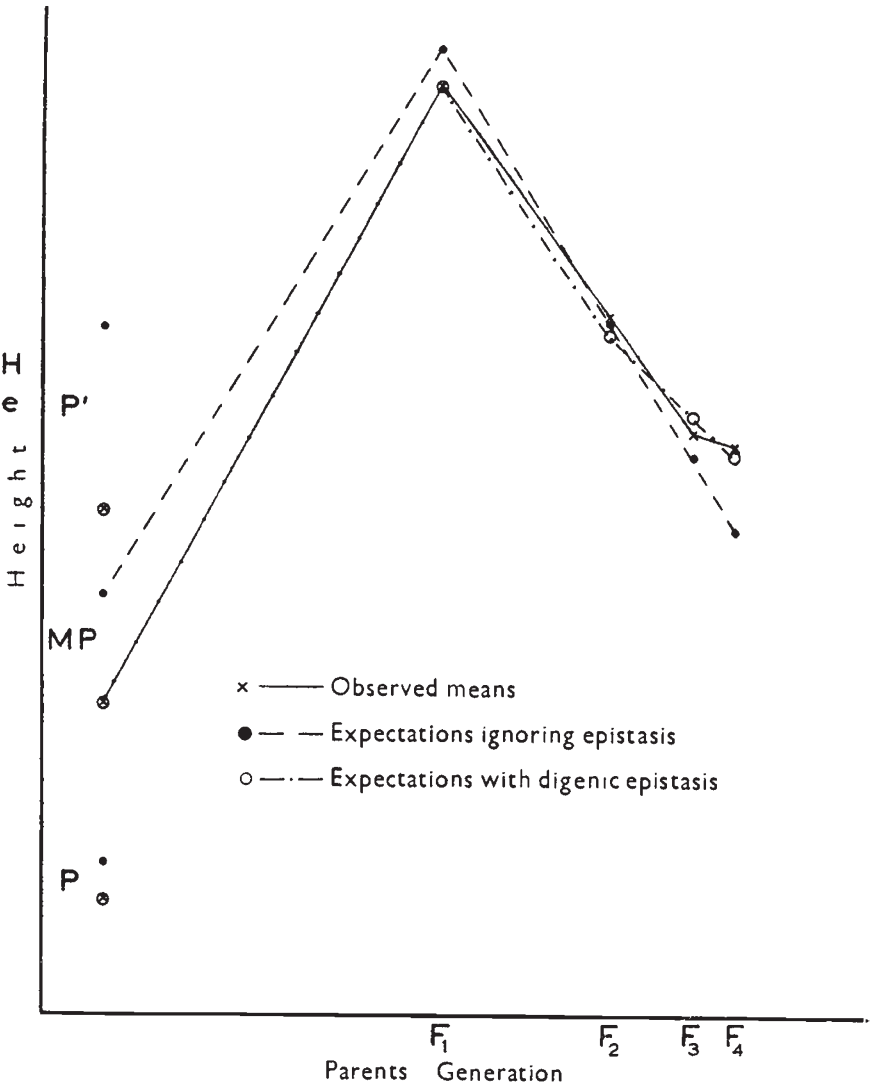

FIG.—Means and expectations in experiment 2. Although the separate parental means are indicated it is the midparent that is joined to the F_1, F_2, F_3 and F_4 means.

Before passing on to other experiments it is interesting to draw together the information about the incidence of epistasis in the *Nicotiana rustica* cross 1 ×2. In 1952 and 1953 this cross was grown in the form of our experiment 1 as part of a diallel experiment of Jinks (1956) while in 1954 and 1955 it was grown by ourselves in the form of our experiment 2 as part of a small diallel experiment. We have reported the results in all these years, except in 1953 when epistasis

is not significant. The incidence of epistasis varies greatly from year to year. In 1953 epistasis is absent—and not through a rise in the environmental variation in that year because genetic and environmental variation are both about 50 per cent. higher than in 1952. The parameters *h*, *i* and *l* are significant and similar in sign in 1952 and 1954 but *i* changes sign and *l* disappears in 1955. The only other parameter common to all years is $d' = d\text{-}j$ which is significantly

TABLE 3

Powers' (1955) Criolle×Sioux tomato cross

	Weight per locule (log scale)		Weight per fruit (log scale)	
	Observation	Difference	Observation	Difference
P	0·3116±0·0168	0·0194±0·0115	1·1558±0·0143	0·0203±0·0101
P'	1·2248±0·0286	0·0170±0·0231	2·1017±0·0250	0·0182±0·0210
F_1	0·8732±0·0222	0·0116±0·0148	1·5431±0·0210	0·0054±0·0150
F_2	0·8020±0·0189	−0·0038±0·0176	1·5775±0·0153	0·0039±0·0142
B	0·5544±0·0157	−0·0225±0·0134	1·3265±0·0119	−0·0101±0·0098
B'	1·0682±0·0167	0·0335±0·0141	1·8479±0·0161	0·0373±0·0142
BS	0·5479±0·0107	−0·0011±0·0082	1·3489±0·0082	−0·0057±0·0061
BS'	0·9835±0·0137	−0·0233±0·0100	1·8132±0·0098	−0·0154±0·0064
	3-parameter model	6-parameter model	3-parameter model	6-parameter model
m	0·8058±0·0068	0·7992±0·0087	1·5736±0·0058	1·5697±0·0071
d	−0·4578±0·0105	−0·4882±0·0196	−0·4740±0·0084	−0·5017±0·0164
h	0·1116±0·0241	0·1592±0·0409	−0·0718±0·0210	−0·0115±0·0333
i	.	0·0468±0·0430	.	0·0655±0·0351
j	.	−0·0454±0·0276	.	−0·0408±0·0238
l	.	−0·0212±0·0955	.	−0·0757±0·0839
χ^2_5	11·51		11·72	
χ^2_2		4·93		3·82

Difference = observed mean − expectation on the 3-parameter model.

negative in both 1952 and 1955 but negligible in 1954. The relation of epistasis to heterosis is similarly variable, epistasis increasing heterosis in 1952 and 1955, decreasing it in 1954 and leaving it unaffected in 1953. Without going into any more detailed argument it is clear that in height in this species epistasis is under the influence of the seasons. Hayman (1957) confirms this by finding a correlation of 0·02 between epistasis in 1952 and 1953 in a diallel of 28 crosses.

(iv) *Experiment* 3: P, P', F_1, F_2, B, B', BS *and* BS'

Powers (1955) investigated number of locules, weight per locule (W/L) and weight per fruit (W/F) in the cross between the tomato varieties Criolle and Sioux. The logarithms of W/L and W/F are normally distributed in non-segregating generations. Table 3 contains the means of these two characters in each family or generation.

The χ^2 with five degrees of freedom supplies some evidence (P =

0·05) for epistasis in both characters. None of the epistatic parameters i, j and l is actually significant in either character but some linear combinations of them must be ; for example, those combinations of i, j and l which form the differences between observation and expectation on the three-parameter model in generations B', BS', and possibly P, are significant.

The similarity between the epistasis in the characters W/L and W/F has a simple explanation in terms of Powers' third character, number of locules (NL). If the non-normality of the parental and F_1 distributions of log(NL) is ignored the χ^2 with five degrees of freedom can be computed for this character, too. This reveals no evidence of epistasis. Now log(W/F) is the sum of log(W/L) and

TABLE 4

Copp's (unpublished) cross 7× Tainui wheat cross

Percentage shattering (angular scale)

	Observation	Difference		3-parameter model	6-parameter model
P	41·0±0·90	−2·71±0·56	m	40·09±0·31	41·26±0·39
P'	36·0±0·90	−3·30±0·56	d	2·20±0·58	0·90±1·34
F_1	34·3±1·05	−4·37±0·71	h	−2·83±1·08	−5·30±1·28
F_2	41·3±0·67	1·21±0·54	i	.	−1·11±1·13
B	41·4±0·95	0·21±0·85	j	.	−1·60±1·49
B'	40·5±0·95	1·52±0·85	l	.	−17·21±4·02
F_3	41·5±0·32	0·71±0·21			
			χ^2_4	50·19	
			χ^2_1		0·01

Difference = observed mean—expectation on the 3-parameter model.

log(NL) so that epistasis in log(W/F) should be similar in nature to epistasis in log(W/L). Dominance, on the other hand, takes different signs in log(W/L) and log(W/F), reflecting the presence of dominance in log(NL). These conclusions agree with Powers' (1955) gene model.

(v) *Experiment* 4: P, P′, F_1, F_2, B, B′ *and* F_3

The wheat cross Cross 7 ×Tainui and descendant generations was grown by Mr L. G. Copp in 1950-51 as part of an experiment at the Crop Research Division, Lincoln, New Zealand. Among the grain characters observed was percentage shattering. This character, measured on an angular scale, was normally distributed in parents and F_1. Table 4 contains the means and variances of each family ; families of the same kind (the two parents or the two backcrosses) have similar variances which are pooled.

The upper half of the table shows that negative dominance amounting almost to heterosis is present in F_1 but this reverses to positive dominance in F_2, F_3 and the backcrosses. This is indicative of the l-type of epistasis which appears in the lower half of the table. The other types of epistasis are of no importance.

4. DISCUSSION

We have presented an investigation of the genetic variation in the family means of four experiments.

All these experiments can be tested for their fit to a simple additive and dominance genetic model. If this fit is bad three of the experiments (2, 3 and 4) can be tested for their fit to a digenic epistatic model in which the genes are not linked.

In the absence of epistasis all the experiments provide estimates of additivity and dominance. When epistasis is present experiments 1, 3 and 4 provide estimates of the three kinds of epistasis as well, but, as we have explained, the measures of additivity and dominance are no longer unique and are valid only in a particular genetic population. This means that the influence of epistasis on, for example, heterosis cannot be fully assessed although a comparison between observation and expectation on the three-parameter model gives some indication of this influence.

It would be a great advantage if an experiment could be designed in which the estimates of m, d and h were independent of epistasis. Quite apart from the difficulty in defining m, d and h in the presence of epistasis it is easy to see from equation (1) that such a design is not possible. In statistical terms the requirement is that m, d and h be orthogonal to i, j and l in the expectations of family means. Since the coefficients of m, i and l are all positive m cannot be orthogonal to i or l.

With the ideal experiment unattainable it becomes more important to assess the accuracy with which the present experiments estimate and separate the various parameters. So as to compare the experiments on a standard basis we shall suppose that all observed means have unit error variances. Table 5 contains variance-correlation matrices of the estimators of the parameters in each of the four experiments. The error variances lie on the diagonals and the error correlations off the diagonals of each matrix.

Experiment 1 is the simplest that permits estimation of all six parameters but the high error variances of $\hat{h}$, $\hat{\imath}$ and $\hat{l}$ show that much less information is available about these parameters than about m, d and j. Further, many of the estimators are highly correlated, especially the pair, $\hat{d}$ and $\hat{\jmath}$, and the trio, $\hat{h}$, $\hat{\imath}$ and $\hat{l}$. The addition of F_3 to the experiment proves to be more rewarding than the addition of BS and BS', especially in the information supplied about h and i. l remains inaccurately estimated in all the experiments. Amongst the correlations, that between $\hat{d}$ and $\hat{\jmath}$ remains high in all three experiments, but all the other correlations are considerably reduced in the larger experiments and especially in the F_3 experiment. In experiment 2, d and j are, of course, fully correlated and cannot be estimated separately but this is the best experiment for estimating h and i. It is also advantageous from a practical point of view with a species such as wheat where much labour is required to produce sufficient seed from a cross.

A more comprehensive measure of the information supplied by an experiment was proposed by Wilks (1932). Just as the reciprocal of the variance of a single variable is a measure of the information about that variable Wilks suggests the use in the multivariate case of the reciprocal of the pth root of the determinant of the variance-covariance matrix of the p variables. This would measure the mean information per variable and is in effect the reciprocal of the geometric mean

TABLE 5

Error variances (diagonal terms) and correlations (off diagonals) of the estimators of m, d, h, i, j *and* l *in the four experiments on the assumption of unit error variances of the observed means. I = mean information per parameter*

Experiment 1

	m	*d*	*h*	*i*	*j*	*l*
m	**1·00**	0·00	−0·79	−0·82	0·00	0·54
d		**2·00**	0·00	0·00	0·89	0·00
h			**25·50**	0·97	0·00	−0·84
i				**24·00**	0·00	−0·89
j					**2·50**	0·00
l	I = 0·5000					**54·00**

Experiment 2

	m	*d′*	*h*	*i*	*l*
m	**0·84**	0·00	0·52	0·51	−0·84
d′		**0·50**	0·00	0·00	0·00
h			**3·27**	0·77	−0·57
i				**3·11**	−0·78
l	I = 0·7019				**42·21**

Experiment 3

	m	*d*	*h*	*i*	*j*	*l*
m	**0·31**	0·00	−0·34	−0·44	0·00	0·03
d		**1·62**	0·00	0·00	0·89	0·00
h			**7·97**	0·91	0·00	−0·71
i				**8·17**	0·00	−0·82
j					**2·29**	0·00
l	I = 0·6734					**31·67**

Experiment 4

	m	*d*	*h*	*i*	*j*	*l*
m	**0·30**	0·00	−0·16	−0·25	0·00	−0·26
d		**2·00**	0·00	0·00	0·89	0·00
h			**4·66**	0·83	0·00	−0·53
i				**4·20**	0·00	−0·72
j					**2·50**	0·00
l	I = 0·6960					**22·55**

of the variances of the variables with due allowance for correlation between the variables. This mean information per variable is included as I in table 5. Experiment 3 supplies about 35 per cent. more information and experiment 4 about 39 per cent. more information than experiment 1. This is in line with our general discussion above and shows that the addition of the single F_3 generation to experiment 1 is on the whole more informative than the addition of the two selfed backcross generations.

One reason for presenting so many experimental results has been to show that epistasis occurs widely and that it may be as important as additivity or dominance in genetic variation. Anderson and Kempthorne (1954) also give an example of our experiment 2 in which epistasis is as important as dominance.

The second reason is to show the variety of epistatic forms. Our i, j and l, representing the influence of the three kinds of epistasis on means, may occur in any combination of sign and magnitude. In particular, experiment 1B shows that epistasis may enhance or diminish heterosis.

The third reason is to investigate the stability of epistatic effects under change of environment. The little evidence from tomato yield in experiment 1A suggests stability of gene action from year to year. Height in *Nicotiana rustica*, however, seems from a comparison of experiments 1B and 2 on the cross 1 ×2 to exhibit stability of dominance but instability of epistasis under seasonal variation. This was also Hayman's (1957) conclusion from 28 crosses grown in two years.

The experiments lead, therefore, to the expected result. Each species and each character has its own mode of action and interaction of the controlling genetic material.

The consequences of our theoretical discussions are not so simple. We have seen that epistasis is an important component of genetic variability and that sufficiently large experiments permit accurate estimation of mean epistatic effects by simple statistical procedures. Although opposing epistases will remain undetected the same is true of dominance and additivity so that our comparisons between the various modes of gene action are on an equitable basis. It should be more informative to measure mean square genetic effects but Hayman (1954*a*, 1955) has shown that the expectations of variances are complicated. Even in experiment 2 the expectations of variances in terms of digenic effects require eight components, and the inclusion of backcross generations would require even more components, unlike the situation with the means where the same six components suffice for all mating combinations descended from two inbred lines. Our measures of epistasis are probably some of the simplest and most reliable that may be devised. However, while we are able to detect and measure epistasis with some confidence, we have uncovered a problem in the proper description of the main effects (additivity and dominance). Earlier we approached this problem through a statistical analogy and now we shall propound a more genetical approach.

Suppose that the two parents P and P' are genetically identical. Then the expectations of all the family or generation means are the same, say m, and the weighted average of these means is the best estimate of the level of expression of the single genotype involved in the experiment. Even if the parents were genetically different this estimate of m would still be a useful norm from which to measure the differences in expression of the various genotypes and, further, this estimate would be unique whatever the mode of gene action. Now suppose that P and P' differ by genes that do not interact non-allelically. Then we may arbitrarily take m to be the expectation of any mean, such as F_2 in our case, or even of a hypothetical mean, such as the midparent, and add appropriate terms in d and h to complete the expectations of the other means. The estimates of d and h are unique but the estimate of m depends on the form of the expectations. Indeed, m no longer represents a norm of gene action but merely a particular (background) population such as F_2, mid-parent, etc. d and h, while nominally defined on the basis of the same

background population are independent of it because of the absence of epistasis. The expectations of the means derived from these m, d and h are also unique in spite of the arbitrary nature of m. Further, even if epistasis did occur amongst the genes by which P and P' differ, the uniqueness of the estimates, ignoring epistasis, of d and h and the corresponding expectations would still be preserved : in this case the expectations would represent the nearest possible non-epistatic system and d and h the main effects in that system. These are the expectations from which we derive the differences in tables 1-4.

The next step is to suppose that P and P' differ by genes exhibiting digenic, but no more complex, epistasis. Then the model of this paper applies : i, j and l are unique measures of epistasis with unique estimates but all three of m, d and h depend, in definition directly, and in their estimates indirectly through the form of the expectations, on an arbitrary background population. The expectations derived from the estimates of the six parameters are unique but m, d and h and expectations derived from their estimates have little use. If we proceed to the fourth stage and admit trigenic epistasis the argument moves up a further step. We add a final simple example from epistacy between two major genes. Here it is not possible to use the description "A is dominant to a" without a qualification such as "only in the presence of the dominant allele B".

The implication of this general discussion is that when epistasis occurs main effects become somewhat intangible. As we have explained here, and as Hayman (1955) has also explained in a slightly different context, the reason lies in our use of ordinary statistical constructs in the genetical situation with its relationships between individuals, laws of segregation, etc., that have no counterpart in ordinary statistical experiments. The complete separation of main effects from epistasis does not seem to be feasible and even a description of gene action jointly in terms of main effects and epistasis seems to be possible only where each gene and each possible genotype in the genetic system can be identified. Our method of considering the deviations of observation from the best-fitting non-epistatic model in terms of the epistasis actually present does, however, give some idea of the relationship between epistasis and additivity and dominance.

5. SUMMARY

Five experiments consisting of various descendants from two inbred lines from various species are described. The means of families or generations are influenced by epistasis, often to as great an extent as by additive or by dominance variation. This epistasis may be in the form of interaction between additive effects, between dominance effects or between additive and dominance effects, and all forms occur in various combinations and with varying sign.

The simplest experiment supplying information on additive, dominance and the three kinds of epistatic variation contains two

inbred lines and their F_1, F_2 and first backcross generations. Not all the genetic parameters are estimated with equal accuracy or without correlation and some improvement in accuracy and independence is gained by adding selfed backcross generations or even more by adding an F_3 generation.

The measurement of additivity and dominance in the presence of epistasis is found to pose a problem. A measure of, say, dominance at a locus depends on the genetic state of other loci interacting with it, so that a unique measure of dominance can only be constructed by arbitrary specification of the state of the other loci. The difficulty can be avoided, but not entirely overcome, by finding the best-fitting (unique) non-epistatic model and considering its deviation from observation in terms of the epistasis present.

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