

INTRODUCTION TO QUANTITATIVE GENETICS

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CHAPTER 14

INBREEDING AND CROSSBREEDING

I. CHANGES OF MEAN VALUE

We turn our attention now to inbreeding, the second of the two ways open to the breeder for changing the genetic constitution of a population. The harmful effects of inbreeding on reproductive rate and general vigour are well known to breeders and biologists, and were mentioned in Chapter 6 as one of the two basic genetic phenomena displayed by metric characters. The opposite, or complementary, phenomenon of hybrid vigour resulting from crosses between inbred lines or between different races or varieties is equally well known, and forms an important means of animal and plant improvement. The production of lines for subsequent crossing in the utilisation of hybrid vigour is one of two main purposes for which inbreeding may be carried out. The other is the production of genetically uniform strains, particularly of laboratory animals, for use in bioassay and in research in a variety of fields. Inbreeding in itself, however, is almost universally harmful and the breeder or experimenter normally seeks to avoid it as far as possible, unless for some specific purpose. Mention should be made here of naturally self-fertilising plants, to which much of the discussion in this chapter is inapplicable. Since inbreeding is their normal mating system they cannot be further inbred: they can, however, be crossed, but they do not regularly show hybrid vigour.

In the treatment of inbreeding given in Chapter 3 the consequences were described in terms of the expected changes of gene frequencies and of genotype frequencies. Here we have to show how the changes of gene and genotype frequencies are expected to affect metric characters. And at the same time we have to consider the observed consequences of inbreeding and crossing, and see what light they throw on the properties of the genes concerned with metric characters. We shall first consider the changes of mean value and then, in the next chapter, the changes of variance resulting from inbreeding and crossbreeding. Finally, in Chapter 16, we shall con-

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sider the combination of selection with inbreeding and crossbreeding by means of which hybrid vigour may be utilised in animal and plant improvement.

INBREEDING DEPRESSION

The most striking observed consequence of inbreeding is the reduction of the mean phenotypic value shown by characters connected with reproductive capacity or physiological efficiency, the phenomenon known as *inbreeding depression*. Some examples of inbreeding depression are given in Table 14.1, from which one can see what sort of characters are subject to inbreeding depression, and—very roughly—the magnitude of the effect. From the results of these and many other studies we can make the generalisation that inbreeding tends to reduce fitness. Thus, characters that form an important component of fitness, such as litter size or lactation in mammals, show a reduction on inbreeding; whereas characters that contribute little to fitness, such as bristle number in *Drosophila*, show little or no change.

In saying that a certain character shows inbreeding depression, we refer to the average change of mean value in a number of lines. The separate lines are commonly found to differ to a greater or lesser extent in the change they show, as, indeed, we should expect in consequence of random drift of gene frequencies. This matter of differentiation of lines will be discussed later when we deal with changes of variance. It is mentioned here only to emphasise the fact that the changes of mean value now to be discussed refer to changes of the mean value of a number of lines derived from one base population. As in our earlier account of inbreeding we have to picture the “whole population” consisting of many lines. The population mean then refers to the whole population and inbreeding depression refers to a reduction of this population mean. Let us now consider the theoretical basis of the change of population mean on inbreeding.

First, we may recall and extend some of the conclusions from Chapter 3, supposing at first that selection does not in any way interfere with the dispersion of gene frequencies. Since the gene frequencies in the population as a whole do not change on inbreeding, any change of the population mean must be attributed to the changes of genotype frequencies. Inbreeding causes an increase in the frequencies of homozygous genotypes and a decrease of heterozygous genotypes.

TABLE 14.1

SOME EXAMPLES OF INBREEDING DEPRESSION

The figures given show approximately the *decrease* of mean phenotypic value per 10 per cent increase of the coefficient of inbreeding: column (1) in absolute units; column (2) as percentage of non-inbred mean; column (3) in terms of the original phenotypic standard deviation (data not available for all characters).

Character	Inbreeding depression per 10% increase of F		
	(1) units	(2) %	(3) / σ_P
<i>Cattle</i> (A. Robertson, 1954)			
Milk-yield	29.6 gal.	3.2	0.17
<i>Pigs</i> (Dickerson <i>et al.</i> 1954)			
Litter size at birth	0.38 young	4.6	0.15
Weight at 154 days	3.64 lb.	2.7	0.12
<i>Sheep</i> (Morley, 1954)			
Fleece weight	0.64 lb.	5.5	0.51
Length of wool	0.12 cm.	1.3	0.14
Body weight at 1 year	2.91 lb.	3.7	0.36
<i>Poultry</i> (Shoffner, 1948)			
Egg-production	9.26 eggs	6.2	—
Hatchability	4.36 %	6.4	—
Body weight	0.04 lb.	0.8	—
<i>Mice</i> (Original data)			
Litter size at birth	0.60 young	8.0	0.28
Weight at 6 weeks (♀♀)	0.58 gm.	2.6	0.26
<i>Drosophila melanogaster</i> (Tantawy and Reeve, 1956)			
Fertility (per pair per day)	2.2 offspring	6.7	—
Viability (egg to adult)	2.6 %	3.7	—
Wing length	2.8 ($\frac{1}{100}$) mm.	1.4	0.80
<i>Drosophila subobscura</i> (Hollingsworth and Smith, 1955)			
Fertility (per pair per day)	6.0 offspring	12.5	—
Egg hatchability	8.3 %	8.3	—

Therefore a change of population mean on inbreeding must be connected with a difference of genotypic value between homozygotes and heterozygotes. Let us now see more precisely how the population mean depends on the degree of inbreeding, which we may conveniently express as the inbreeding coefficient, F .

Consider a population, subdivided into a number of lines, with a coefficient of inbreeding, F . The expression for the population mean is derived by putting together the reasoning set out in Tables 3.1 and 7.1, in the following way. Table 14.2 shows the three genotypes of a two-allele locus with their genotypic frequencies in the whole population. These frequencies come from Table 3.1, $\bar{p}$ and $\bar{q}$ being the gene frequencies in the whole population. Then the third column gives the genotypic values assigned as in Fig. 7.1. The value and

TABLE 14.2

<i>Genotype</i>	<i>Frequency</i>	<i>Value</i>	<i>Frequency × Value</i>
A_1A_1	$\bar{p}^2 + \bar{p}\bar{q}F$	$+a$	$\bar{p}^2a + \bar{p}\bar{q}aF$
A_1A_2	$2\bar{p}\bar{q} - 2\bar{p}\bar{q}F$	d	$2\bar{p}\bar{q}d - 2\bar{p}\bar{q}dF$
A_2A_2	$\bar{q}^2 + \bar{p}\bar{q}F$	$-a$	$-\bar{q}^2a - \bar{p}\bar{q}aF$

$$\begin{aligned}\text{Sum} &= a(\bar{p} - \bar{q}) + 2d\bar{p}\bar{q} - 2d\bar{p}\bar{q}F \\ &= a(\bar{p} - \bar{q}) + 2d\bar{p}\bar{q}(1 - F)\end{aligned}$$

frequency of each genotype are multiplied together in the right-hand column, the summation of which gives the contribution of this locus to the population mean. Thus, referring still to the effects of a single locus, we find that a population with inbreeding coefficient F has a mean genotypic value:

$$\begin{aligned}M_F &= a(\bar{p} - \bar{q}) + 2d\bar{p}\bar{q}(1 - F) && \text{.....(14.1)} \\ &= M_0 - 2d\bar{p}\bar{q}F && \text{.....(14.2)}\end{aligned}$$

where M_0 is the population mean before inbreeding, from equation 7.2. The change of mean resulting from inbreeding is therefore $-2d\bar{p}\bar{q}F$. This shows that a locus will contribute to a change of mean value on inbreeding only if d is not zero; in other words if the value of the heterozygote differs from the average value of the homozygotes. This conclusion, though demonstrated in detail only for two alleles at a locus, is equally valid for loci with more than two alleles. The following general conclusions can therefore be drawn: that a change of mean value on inbreeding is a consequence of dominance at the loci concerned with the character, and that the direction of the change

is toward the value of the more recessive alleles. The dominance may be partial or complete, or it may be overdominance; all that is necessary for a locus to contribute to a change of mean is that the heterozygote should not be exactly intermediate between the two homozygotes. Equation 14.2 shows also that the magnitude of the change of mean depends on the gene frequencies. It is greatest when $\bar{p}\bar{q}$ is maximal: that is, when $\bar{p} = \bar{q} = \frac{1}{2}$. Genes at intermediate frequencies therefore contribute more to a change of mean than genes at high or low frequencies, other things being equal.

Now let us consider the combined effect of all the loci that affect the character. In so far as the genotypic values of the loci combine additively, the population mean is given by summation of the contributions of the separate loci, thus:

$$M_F = \Sigma a(\bar{p} - \bar{q}) + 2(\Sigma d\bar{p}\bar{q})(1 - F) \quad \dots\dots(14.3)$$

$$= M_0 - 2F\Sigma d\bar{p}\bar{q} \quad \dots\dots(14.4)$$

and the change of mean on inbreeding is $-2F\Sigma d\bar{p}\bar{q}$.

These expressions show what are the circumstances under which a metric character will show a change of mean value on inbreeding. The chief one is if the dominance of the genes concerned is preponderantly in one direction; i.e. if there is directional dominance. If the genes that increase the value of the character are dominant over their alleles that reduce the value, then inbreeding will result in a reduction of the population mean, i.e. a change in the direction of the more recessive alleles. The contribution of each locus, however, depends also on its gene frequencies, those with intermediate frequencies having the greatest effect on the change of mean value.

We have now reached two conclusions about the effects of inbreeding, one from observation—that inbreeding reduces fitness; the other from theory—that the change is in the direction of the more recessive alleles. Putting these two conclusions together leads to the generalisation, already familiar from Mendelian genetics, that deleterious alleles tend to be recessive.

Another conclusion that can be drawn from equation 14.4 is that when loci combine additively the change of mean on inbreeding should be directly proportional to the coefficient of inbreeding. In other words the change of mean should be a straight line when plotted against F . Two examples of experimentally observed inbreeding depression are illustrated in Fig. 14.1.

On the whole the observed inbreeding depression does tend to be

linear with respect to F , and this might be taken as evidence that epistatic interaction between loci is not of great importance. There are, however, several practical difficulties that stand in the way of drawing firm conclusions from observations of the rate of inbreeding depression. One is that as inbreeding proceeds and reproductive capacity deteriorates, it soon becomes impossible to avoid the loss of

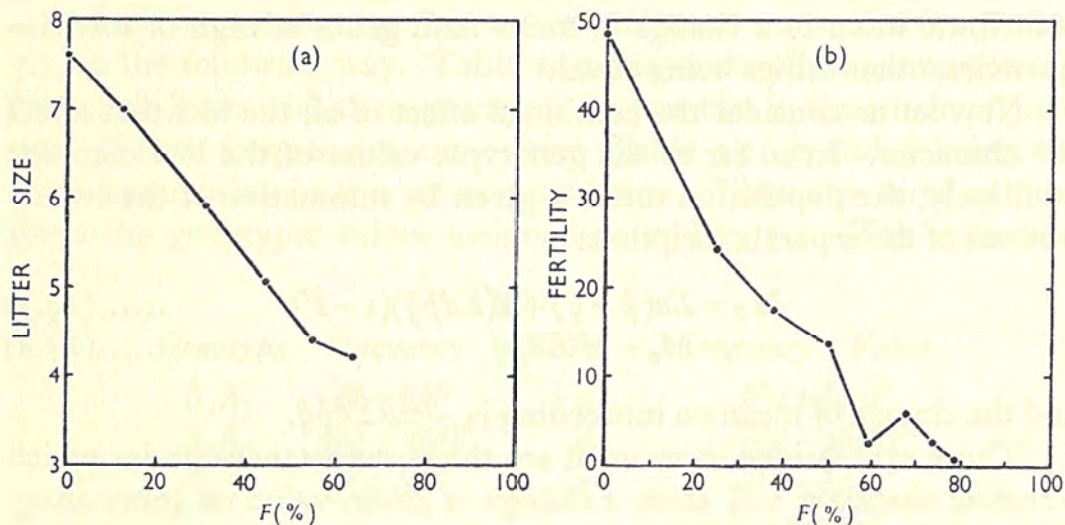


FIG. 14.1. Examples of inbreeding depression affecting fertility. (a) Litter-size in mice (original data). Mean number born alive in 1st litters, plotted against the coefficient of inbreeding of the litters. The first generation was by double-first-cousin mating; thereafter by full-sib mating. No selection was practised. (b) Fertility in *Drosophila subobscura*. Mean number of adult progeny per pair per day, plotted against the inbreeding coefficient of the parents. Consecutive full-sib matings. (Redrawn from Hollingsworth & Smith, 1955.)

some lines. The survivors are then a selected group to which the theoretical expectations no longer apply. Thus precise measurement of the rate of inbreeding depression can generally be made only over the early stages, before the inbreeding coefficient reaches high levels. Another difficulty, met with particularly in the study of mammals, arises from maternal effects. Maternal qualities are among the most sensitive characters to inbreeding depression. The effect of inbreeding on another character that is influenced by maternal effects is therefore two-fold: part being attributable to the inbreeding of the individuals measured and part to the inbreeding in the mothers. So the relationship between the character measured and the coefficient of inbreeding cannot be depicted in any simple manner. In conse-

quence of these difficulties reliable conclusions cannot easily be drawn from the exact form of the inbreeding depression observed in experiments.

EXAMPLE 14.1. The complications arising from maternal effects may be illustrated by litter size in pigs and mice. Litter size is a composite character, which is partly an attribute of the mother and partly an attribute of the young in the litter. It is therefore influenced both by the inbreeding of the mother and by the inbreeding of the young, and these two influences are difficult to disentangle in practice. Studies on pigs (Dickerson *et al.*, 1954) have shown that the reduction of litter size due to inbreeding in the mother alone is about 0.20 young per 10 per cent of inbreeding; and the reduction due to inbreeding in the young alone is about 0.17 young per 10 per cent of inbreeding. Thus the effects of inbreeding in the mother and in the young are about equally important. A small experiment with mice (original data) gave much the same picture. A rough separation of the effects of inbreeding in the mother and in the young was made by means of crosses between lines after 2 or 3 generations of sib mating. (The justification for regarding this as a measure of the inbreeding depression will be explained in the next section.) The mean litter sizes, arranged according to the coefficient of inbreeding of the mothers and of the young, are given in the table.

		<i>Inbreeding coefficient of mothers</i>		
		0%	37.5%	50%
<i>Inbreeding coefficient of young</i>	0%	8.2	7.5	7.3
	50%	—	6.3	—
	59%	—	—	5.8

The three comparisons in the first row show the effect of inbreeding in the mothers, and give values of 0.19, 0.18 and 0.16 for the reduction of litter size per 10 per cent of inbreeding. The comparisons in the second and third column show the effect of inbreeding in the young, and give values of 0.24 and 0.25 for the reduction per 10 per cent of inbreeding. Thus inbreeding in the young had rather more effect than inbreeding in the mother. These results, however, should not be taken as being characteristic of mice in general.

The effect of selection. The neglect of selection during inbreeding is an unrealistic omission because natural selection cannot be wholly avoided even in laboratory experiments. Since inbreeding tends to reduce fitness, natural selection is likely to oppose the inbreeding process by favouring the least homozygous individuals.

The balance between selection and the dispersion of gene frequencies was discussed in Chapter 4, and the only further point that need be added here is that the operation of natural selection makes the inbreeding depression dependent on the rate of inbreeding. One must distinguish between the state of dispersion of gene frequencies and the coefficient of inbreeding as computed from the population size or the pedigree relationships. The state of dispersion is what determines the amount of inbreeding depression; the coefficient of inbreeding is a measure of the state of dispersion only in the absence of selection. When selection operates, the state of dispersion will be less than that indicated by the coefficient of inbreeding, and the discrepancy between the two will be greater when the rate of inbreeding is slower, because the selection will then be relatively more potent. Therefore one must expect the inbreeding depression caused by a given increase of the computed coefficient of inbreeding to be less when inbreeding is slow than when it is rapid.

HETEROSIS

Complementary to the phenomenon of inbreeding depression is its opposite, "hybrid vigour" or *heterosis*. When inbred lines are crossed, the progeny show an increase of those characters that previously suffered a reduction from inbreeding. Or, in general terms, the fitness lost on inbreeding tends to be restored on crossing. That the phenomenon of heterosis is simply inbreeding depression in reverse can be seen by consideration of how the population mean depends on the coefficient of inbreeding, as shown in equation 14.4. Consider, as before, a population subdivided into a number of lines. If the lines are crossed at random, the average coefficient of inbreeding in the cross-bred progeny reverts to that of the base population. Thus, if a number of crosses are made at random between the lines, the mean value of any character in the cross-bred progeny is expected to be the same as the population mean of the base population. In other words, the heterosis on crossing is expected to be equal to the depression on inbreeding. Furthermore, if the population is continued after the crossing by random mating among the cross-bred and subsequent generations, the coefficient of inbreeding will remain unchanged, and the population mean is consequently expected to remain at the level of the base population. We may, thus, make the following generalisa-

tion on theoretical grounds: that, in the absence of selection, inbreeding followed by crossing of the lines in a large population is not expected to make any permanent change in the population mean.

EXAMPLE 14.2. An experiment with mice (R. C. Roberts, unpublished) was designed to test the theoretical expectation that in the absence of selection the heterosis on crossing should be equal to the depression on inbreeding. The character studied was litter size. Thirty lines taken from a random-bred population were inbred by 3 consecutive generations of full-sib mating, bringing the coefficient of inbreeding up to 50 per cent in the litters and 37.5 per cent in the mothers. No selection was practised during the inbreeding, and only 2 of the 30 lines were lost as a consequence of their inbreeding depression.

	<i>Litter size</i>
Before inbreeding	8.1
Inbred (litters: $F = 50\%$)	5.7
Cross-bred	8.5

After the third generation of inbreeding, crosses were made at random between the lines, and in the next generation crosses between the F_1 's were made so as to give cross-bred mothers with non-inbred young. The mean litter sizes observed at the different stages are given in the table. The inbreeding depression was 2.4 and the heterosis 2.8; the two are equal within the limits of experimental error.

Single crosses. The foregoing theoretical conclusions refer to the average of a large number of crosses between lines derived from a single base population. In practice, however, one is often interested in a somewhat different problem, namely the heterosis shown by a particular cross between two lines, or between two populations which may have no known common origin. To refer the changes of mean value to changes of inbreeding coefficient would be inappropriate under these circumstances, and the theoretical basis of the heterosis is better expressed in terms of the gene frequencies in the two lines. We may recall from Chapter 3 that inbreeding leads to a dispersion of gene frequencies among the lines, the lines becoming differentiated in gene frequency as inbreeding proceeds; and the coefficient of inbreeding is a means of expressing the degree of differentiation (equation 3.14). In turning from the inbreeding coefficient to the gene frequencies as a basis for discussion we are therefore turning from the general, or average, consequence of crossing, to the particular circumstances in two lines.

Let us, then, consider two populations, referred to as the "parent populations," both random-bred though not necessarily large. The parent populations are crossed to produce an F_1 or "first cross-bred generation," and the F_1 individuals are mated together at random to produce an F_2 or "second cross-bred generation." The amount of heterosis shown by the F_1 or the F_2 will be measured as the deviation from the mid-parent value, i.e. as the difference from the mean of the two parent populations. First consider the effects of a single locus with two alleles whose frequencies are p and q in one population, and p' and q' in the other. Let the difference of gene frequency between the two populations be y , so that $y = p - p' = q' - q$. The algebra is then simplified by writing the gene frequencies p' and q' in the second population as $(p - y)$ and $(q + y)$. Let the genotypic values be $a, d, -a$, as before. They are assumed to be the same in the two populations, epistatic interaction being disregarded. We have to find the mean of each parent population and the mid-parent value; then the mean of the F_1 and the mean of the F_2 . The parental means, M_{P_1} and M_{P_2} , are found from equation 7.2. They are

$$\begin{aligned} M_{P_1} &= a(p - q) + 2dpq \\ M_{P_2} &= a(p - y - q - y) + 2d(p - y)(q + y) \\ &= a(p - q - 2y) + 2d[pq + y(p - q) - y^2] \end{aligned}$$

The mid-parent value is

$$\begin{aligned} M_{\bar{P}} &= \frac{1}{2}(M_{P_1} + M_{P_2}) \\ &= a(p - q - y) + d[2pq + y(p - q) - y^2] \quad \dots\dots(14.5) \end{aligned}$$

When the two populations are crossed to produce the F_1 , individuals taken at random from one population are mated to indi-

TABLE 14.3
FREQUENCIES OF ZYGOTES IN THE F_1

		Gametes from P_1	
		A_1	A_2
		p	q
Gametes from P_2 }	A_1	$p(p - y)$	$q(p - y)$
	A_2	$p(q + y)$	$q(q + y)$

viduals taken at random from the other population. This is equivalent to taking genes at random from the two populations, as shown in Table 14.3. The F_1 is therefore constituted as follows:

Genotypes	A_1A_1	A_1A_2	A_2A_2
Frequencies	$p(p-y)$	$2pq+y(p-q)$	$q(q+y)$
Genotypic values	a	d	$-a$

The mean genotypic value of the F_1 is therefore:

$$\begin{aligned} M_{F_1} &= a(p^2 - py - q^2 - qy) + d[2pq + y(p - q)] \\ &= a(p - q - y) + d[2pq + y(p - q)] \end{aligned} \quad \text{.....(14.6)}$$

The amount of heterosis, expressed as the difference between the F_1 and the mid-parent values, is obtained by subtracting equation 14.5 from equation 14.6:

$$\begin{aligned} H_{F_1} &= M_{F_1} - M_{\bar{P}} \\ &= dy^2 \end{aligned} \quad \text{.....(14.7)}$$

Thus heterosis, just like inbreeding depression, depends for its occurrence on dominance. Loci without dominance (i.e. loci for which $d=0$) cause neither inbreeding depression nor heterosis. The amount of heterosis following a cross between two particular lines or populations depends on the square of the difference of gene frequency (y) between the populations. If the populations crossed do not differ in gene frequency there will be no heterosis, and the heterosis will be greatest when one allele is fixed in one population and the other allele in the other population.

Now consider the joint effects of all loci at which the two parent populations differ. In so far as the genotypic values attributable to the separate loci combine additively, we may represent the heterosis produced by the joint effects of all the loci as the sum of their separate contributions. Thus the heterosis in the F_1 is

$$H_{F_1} = \sum dy^2 \quad \text{.....(14.8)}$$

If some loci are dominant in one direction and some in the other their effects will tend to cancel out, and no heterosis may be observed, in spite of the dominance at the individual loci. The occurrence of heterosis on crossing is therefore, like inbreeding depression, dependent on directional dominance, and the absence of heterosis is not sufficient ground for concluding that the individual loci show no dominance.

Before we go on to consider the F_2 it is perhaps worth noting that the formulation of the heterosis in terms of the square of the difference of gene frequency, in equations 14.7 and 14.8, is quite in line

with the previous formulation of the inbreeding depression in terms of the coefficient of inbreeding. If we envisage once more the whole population subdivided into lines, and we suppose pairs of lines to be taken at random, then the mean squared difference of gene frequency between the pairs of lines will be equal to twice the variance of gene frequency among the lines. That is: $(\bar{y}^2) = 2\sigma_q^2$. And, by equation 3.14, $2\sigma_q^2 = 2\bar{p}\bar{q}F$. Therefore the mean amount of heterosis shown by crosses between random pairs of lines is equal to the inbreeding depression as given in equation 14.2, though of opposite sign.

Now let us consider the F_2 of a particular cross of two parent populations, the F_2 being made by random mating among the individuals of the F_1 . In consequence of the random mating, the genotype frequencies in the F_2 will be the Hardy-Weinberg frequencies corresponding to the gene frequency in the F_1 . The mean genotypic value of the F_2 is then easily derived by application of equation 7.2. The gene frequency in the F_1 , being the mean of the gene frequencies in the two parent populations, is $(p - \frac{1}{2}y)$ for one allele, and $(q + \frac{1}{2}y)$ for the other. Putting these gene frequencies in place of p and q respectively in equation 7.2 gives the mean genotypic value of the F_2 as:

$$\begin{aligned} M_{F_2} &= a(p - \tfrac{1}{2}y - q - \tfrac{1}{2}y) + 2d(p - \tfrac{1}{2}y)(q + \tfrac{1}{2}y) \\ &= a(p - q - y) + d[2pq + y(p - q) - \tfrac{1}{2}y^2] \quad \dots\dots(14.9) \end{aligned}$$

The amount of heterosis shown by the F_2 is the difference between the F_2 and mid-parent values. So, from equations 14.5 and 14.9,

$$\begin{aligned} H_{F_2} &= M_{F_2} - M_{\bar{F}} \\ &= \tfrac{1}{2}dy^2 \\ &= \tfrac{1}{2}H_{F_1} \quad \dots\dots(14.10) \end{aligned}$$

We find therefore that the heterosis shown by the F_2 is only half as great as that shown by the F_1 . In other words, the F_2 is expected to drop back half-way from the F_1 value toward the mid-parent value. At first sight this conclusion may seem to contradict the one arrived at earlier, when we were considering crosses between many lines, the F_1 and F_2 means then being equal. The difference between the two situations is that an F_2 made by random mating among a large number of different crosses has the same inbreeding coefficient as the F_1 . But an F_2 made from an F_1 derived from a single cross has inevitably an increased inbreeding coefficient. If the inbreeding coefficient is

worked out in the manner described in Example 5.2, it will be found to be half the inbreeding coefficient of the parent lines. The change of mean from F_1 to F_2 may therefore be regarded as inbreeding depression. It cannot be overcome by having a large number of parents of the F_2 because the restriction of population size that causes the inbreeding has already been made in the single cross of only two lines, or parent populations. There need, however, be no further rise of the inbreeding coefficient in the F_3 and subsequent generations. Provided, therefore, that there is no other reason for the gene frequency to change, the population mean will be the same in the generations following as in the F_2 .

That the heterosis expected in the F_2 is half that found in the F_1 is equally true when the joint effects of all loci are considered, provided that epistatic interaction is absent. The conclusion for a single locus was based on the principle that Hardy-Weinberg equilibrium is attained by a single generation of random mating. It will be remembered from Chapter 1 (p. 19), however, that this is not true with respect to genotypes at more than one locus considered jointly. Therefore if there is epistatic interaction, the population mean will not reach its equilibrium value in the F_2 , but will approach it more or less rapidly according to the number of interacting loci and the closeness of the linkage between them. The existence of epistatic interaction is intimately connected with the scale of measurement, but this matter will not be discussed until Chapter 17. Here we need only note that for reasons connected with the scale of measurement the halving of the heterosis in the F_2 expected on theoretical grounds is not often found at all exactly in practice, though the F_2 usually falls somewhere between the F_1 and mid-parent values. Some examples from plants of the heterosis observed in the F_1 and F_2 generations are illustrated in Fig. 14.2. It will be noticed that with some of the characters shown, the F_1 and F_2 are lower in value than the mid-parent, and the heterosis is consequently negative in sign. This is in no way inconsistent with our definition of heterosis as the difference between the F_1 or F_2 and the mid-parent value. The sign of the difference depends simply on the nature of the measurement. For example, the character "days to first fruit," represented in the lower graphs, shows heterosis of negative sign: but if the character were called "speed of development" and expressed as a reciprocal of time the heterosis would be positive in sign.

The relative amount of heterosis observed in the F_1 and F_2

generations is complicated also by the existence of maternal effects, particularly in mammals. A character subject to a maternal effect,

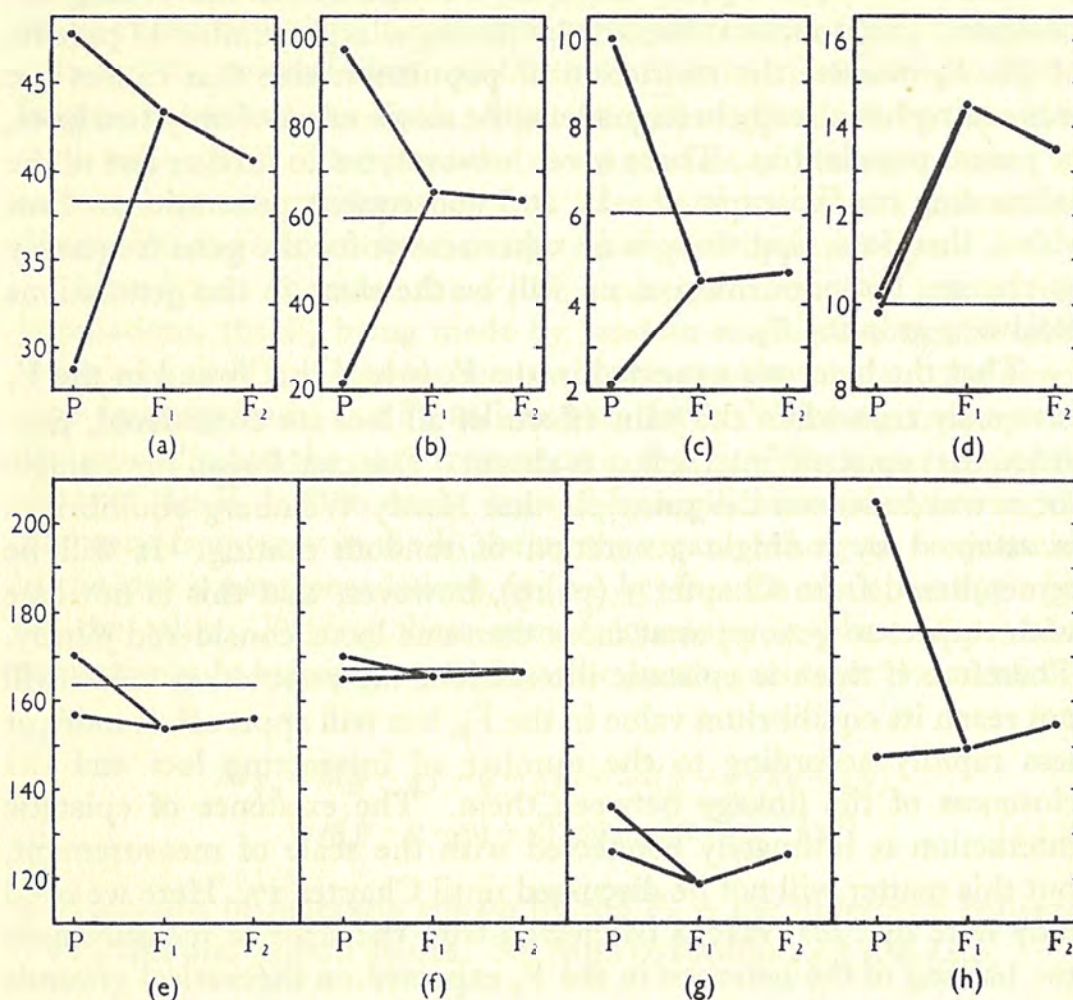


FIG. 14.2. Some illustrations of heterosis observed in crosses between pairs of highly inbred strains of plants. The points show the mean values of the two parent strains, the F₁ and the F₂ generations. The mid-parent values are shown by horizontal lines. Graph (a) refers to tobacco, *Nicotiana rustica* (data from Smith, 1952). All the other graphs refer to tomatoes, *Lycopersicon* (Data from Powers, 1952). The characters represented are:

- (a) Height of plant (in.)
- (b) Mean weight of one fruit (gm.)
- (c) Number of locules per fruit
- (d) Mean weight per locule (gm.)
- (e)–(h) Mean time in days between the planting of the seed and the ripening of the first fruit, in 4 different crosses.

such as litter size, is divided between two generations. The maternally determined component of the character may be expected to follow the

same general pattern of heterosis in the F_1 and F_2 as we have just discussed, but it will be one generation out of phase with the non-maternal part of the character. Thus the heterosis observed in the F_1 is attributable to the non-maternal part, the maternal effect being still at the inbred level. In the F_2 , however, the non-maternal part will lose half the heterosis as explained above, but the maternal effect will now show the full effect of its heterosis since the mothers are now in the F_1 stage. This rather complicated situation may perhaps be more

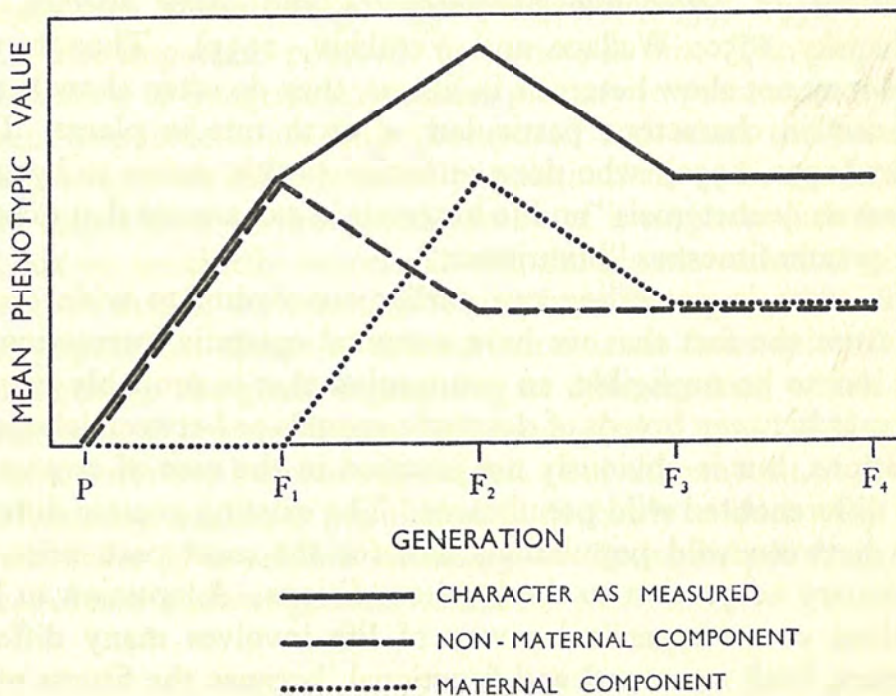


FIG. 14.3. Diagram of the heterosis expected in a character subject to a maternal effect, when two lines are crossed and the F_2 is made by random mating among the F_1 . The maternal and non-maternal components of the character separately are here supposed to show equal amounts of heterosis, and to combine by simple addition to give the character as it is measured.

readily grasped from the diagrammatic representation in Fig. 14.3. As a result of maternal effects, therefore, the loss of heterosis in the F_2 and subsequent generations is usually less noticeable with animals than with plants, and experiments of great precision would be required to detect any regular pattern.

Wide crosses. We have seen that the amount of heterosis shown by a particular cross depends, among other things, on the differences of gene frequency between the two populations crossed. This would seem to indicate that the amount of heterosis would increase with the

degree of genetic differentiation between the two populations and would be limited only by the barrier of interspecific sterility. This, however, is not true. Crosses between subspecies, or between local races, taken from the wild often fail to show heterosis, particularly in characters closely related to fitness which show heterosis in crosses between less differentiated laboratory populations. Indeed the F_1 's of wide crosses are often less fit than the parent populations. Much of the evidence about such crosses comes from studies of wild populations of *Drosophila pseudoobscura* and other species, (see Dobzhansky, 1950; Wallace and Vetukhiv, 1955). Though wide crosses may not show heterosis in fitness, they do often show heterosis in certain characters, particularly growth rate in plants. Dobzhansky (1950, 1952), who drew attention to this, refers to heterosis in fitness as "euheterosis" and to heterosis in a character that does not confer greater fitness as "luxuriance."

The error in extending our earlier conclusion to wide crosses arises from the fact that we have assumed epistatic interaction between loci to be negligible, an assumption that is probably justified for crosses between breeds of domestic animals or between laboratory populations, but is obviously not justified in the case of crosses between differentiated wild populations. The existing genetic differentiation between wild populations has, for the most part, arisen by evolutionary adaptation to the local conditions. Adaptation to local conditions or to a particular way of life involves many different characters, both structural and functional, because the fitness of the organism depends on the harmonious interrelations of all its parts. If two populations adapted to different ways of life are crossed, the cross-bred individuals will be adapted to neither, and will consequently be less fit than either of the parent populations. The effect of this evolutionary adaptation on the genetic structure of the populations is as follows. The genes A_1 and B_1 , say, are selected in one population because together they increase fitness, though either one separately may not; while, in another population living under different conditions, the genes A_2 and B_2 are selected for similar reasons. In respect of fitness, therefore, there is epistatic interaction between these two loci. But if these pairs of genes become fixed throughout the two populations, A_1 and B_1 in one and A_2 and B_2 in the other, and so become part of their constant genetic structure, the variation arising from this interaction will disappear. Within any one population, therefore, we may find very little epistatic variation, and the interac-

tion will become apparent as a cause of variation between individuals only in a cross-bred population in which there is segregation at both interacting loci.

The idea that the genetic structure of a natural population evolves as a whole, so that the selection pressure on any one locus is dependent on the alleles present at many of the other loci, is expressed in the terms "coadaptation" and "integration," used to describe the genetic structure of natural populations. (For general discussions of these concepts, see Dobzhansky, 1951b; Lerner, 1954, 1958; Wright, 1956.) The important point for us to note is this. The property of coadaptation, or integration, assumes primary importance only when different populations are to be compared and when the results of crossing adaptively differentiated populations are to be studied; it is of less importance in the genetic study of a single population. In this book we are chiefly concerned with the genetic variation within a population: that is, the variation arising from the segregation of genes in the population. Some of this variation arises from epistatic interaction between the genes segregating at different loci, which is the raw material, as it were, from which coadaptation could evolve if the population were to become subdivided. But the amount of this epistatic variation within a population is probably seldom very large, and moreover it is seldom necessary to distinguish it from other sources of non-additive genetic variance.

CHAPTER 15

INBREEDING AND CROSSBREEDING:

II. CHANGES OF VARIANCE

The effect of inbreeding on the genetic variance of a metric character is apparent, in its general nature, from the description of the changes of gene frequency given in Chapter 3. Again, we have to imagine the whole population, consisting of many lines. Under the dispersive effect of inbreeding, or random drift, the gene frequencies in the separate lines tend toward the extreme values of 0 or 1, and the lines become differentiated in gene frequency. Since the mean genotypic value of a metric character depends on the gene frequencies at the loci affecting it, the lines become differentiated, or drift apart, in mean genotypic value. And, since the genetic components of variance diminish as the gene frequencies tend toward extreme values (see Fig. 8.1), the genetic variance within the lines decreases. The general consequence of inbreeding, therefore, is a redistribution of the genetic variance; the component appearing between the means of lines increases, while the component appearing within the lines decreases. In other words, inbreeding leads to genetic differentiation between lines and genetic uniformity within lines. The differentiation is illustrated from experimental data in Fig. 15.1.

The subdivision of an inbred population into lines introduces an additional observational component of variance, the between-line component, and it is not surprising that this adds a considerable complication to the theoretical description of the components of genetic variance. Indeed, a full theoretical treatment of the redistribution of variance has not yet been achieved. Here we shall attempt no more than a brief description of the main outlines, and for this we shall have to make some simplifications. In particular we shall entirely neglect the interaction component of genetic variance arising from epistasis. For detailed treatment of various aspects of the problem, and for references, see Kempthorne (1957, Ch. 17). After this description of the redistribution of genetic variance we shall consider changes of environmental variance. The greater sensitivity

of inbred individuals to environmental sources of variation was mentioned earlier, in Chapter 8. This phenomenon interferes with the experimental study of the changes of variance, and until it is better understood we cannot put much reliance on the theoretical

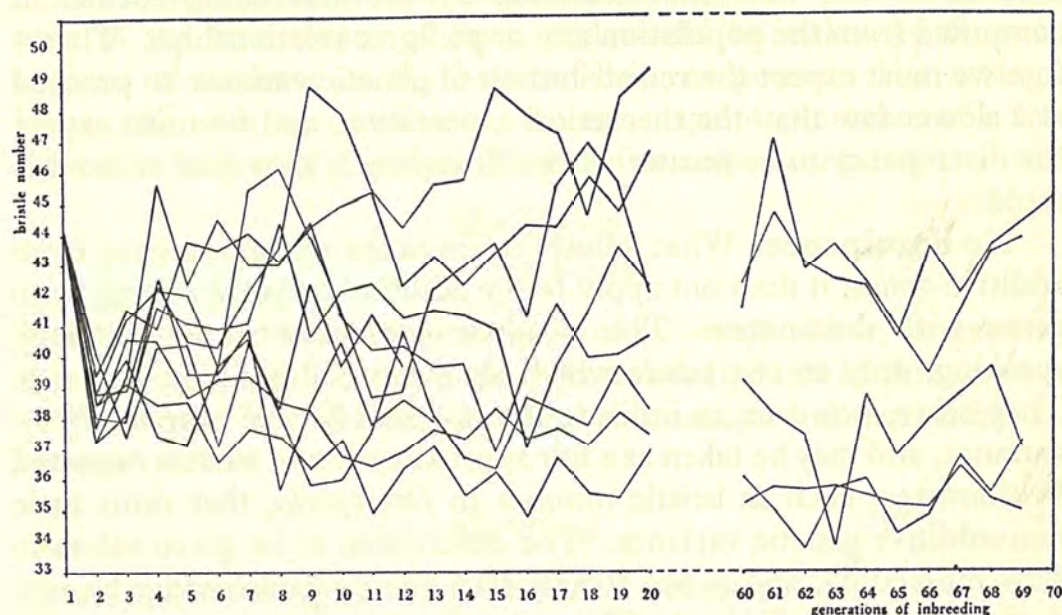


FIG. 15.1. Differentiation between lines by random drift, shown by abdominal bristle number in *Drosophila melanogaster*. The graphs show the mean bristle number in each of 10 lines during full-sib inbreeding without artificial selection. (From Rasmuson, 1952; reproduced by courtesy of the author and the editor of *Acta Zoologica*.)

expectations concerning variance being manifest in the observable phenotypic variance. Finally, in this chapter, we shall discuss the use of inbred animals for experimental purposes.

REDISTRIBUTION OF GENETIC VARIANCE

The redistribution of variance arising from additive genes (i.e. genes with no dominance) is easily deduced. This is because with additive genes the proportions in which the original variance is distributed within and between lines does not depend on the original gene frequencies. When there is dominance, however, we cannot deduce the changes of variance without a knowledge of the initial gene frequencies. This not only adds considerably to the mathematical complexity, but it renders a general solution impossible. We shall

first consider the case of additive genes, and then very briefly indicate the conclusions arrived at for dominant genes. The effect of selection will not be specifically discussed. We need only note that natural selection will tend to render the actual state of dispersion of gene frequencies less than that indicated by the inbreeding coefficient computed from the population size or pedigree relationships. Therefore we must expect the redistribution of genetic variance to proceed at a slower rate than the theoretical expectation, and we must expect the discrepancy to be greater when inbreeding is slow than when it is rapid.

No dominance. What follows refers to the variance arising from additive genes: it does not apply to the additive variance arising from genes with dominance. The conclusions therefore apply, strictly speaking, only to characters which show no non-additive variance. They serve, however, to indicate the general effect of inbreeding on variance, and may be taken as a fair approximation to what is expected of characters such as bristle number in *Drosophila*, that show little non-additive genetic variance. The description to be given refers to slow inbreeding, and is not strictly true of rapid inbreeding by sib-mating or self-fertilisation. The redistribution of the variance under rapid inbreeding is, however, not very different except in the first few generations.

Consider first a single locus. When there is no dominance the genotypic variance in the base population, given in equation 8.7, becomes

$$V_G = 2p_0q_0a^2$$

The variance within any one line is

$$V_G = 2pq a^2$$

where p and q are the gene frequencies in that line. The mean variance within lines is

$$V_{Gw} = 2(\overline{pq})a^2$$

where $(\overline{pq})$ is the mean value of pq over all lines. Now, $2(\overline{pq})$ is the overall frequency of heterozygotes in the whole population, which, by Table 3.1, is equal to $2p_0q_0(1-F)$, where F is the coefficient of inbreeding. Therefore

$$\begin{aligned} V_{Gw} &= 2p_0q_0a^2(1-F) \\ &= V_G(1-F) \end{aligned}$$

and this remains true when summation of the variances is made over all loci. Thus the within-line variance is $(1 - F)$ times the original variance, and as F approaches unity the within-line variance approaches zero.

Now let us consider the between-line variance. This is the variance of the true means of lines, and would be estimated from an analysis of variance as the between-line component. For a single locus, still with no dominance, the mean genotypic value of a line with gene frequency p and q is obtained from equation 7.2 as

$$\begin{aligned} M &= a(p - q) \\ &= a(1 - 2q) \end{aligned}$$

Thus we want to find the variance of $(a - 2aq)$. Now, in general, $\sigma^2_{(X-Y)} = \sigma_X^2 + \sigma_Y^2$, if X and Y are uncorrelated. Since in this case a is constant from line to line (epistasis being assumed absent) it has no variance, and so

$$\sigma_M^2 = \sigma_{(2aq)}^2$$

Again, in general, $\sigma_{(KX)}^2 = K^2 \sigma_X^2$ when K is a constant. So

$$\begin{aligned} \sigma_M^2 &= 4a^2 \sigma_q^2 \\ &= 4a^2 p_0 q_0 F \quad (\text{from 3.14}) \\ &= 2F V_G \end{aligned}$$

and this also remains true when summation is made over all loci. Thus the between-line genetic variance is $2F$ times the genetic variance in the base population.

The partitioning of the genetic variance into components as explained above is summarised in Table 15.1. The total genetic

TABLE 15.1

Partitioning of the variance due to additive genes in a population with inbreeding coefficient F , when the variance due to additive genes in the base population is V_G .

Between lines	$2FV_G$
Within lines	$(1 - F)V_G$
Total	$(1 + F)V_G$

variance in the whole population is the sum of the within-line and between-line components, and is equal to $(1 + F)$ times the original genetic variance. (This is true also of close inbreeding.) Thus when inbreeding is complete the genetic variance in the population as a

whole is doubled, and all of it appears as the between-line component.

The genetic variance within lines, before inbreeding is complete, is partitioned within and between the families of which the lines are composed. Under slow inbreeding with random mating within the lines, it is partitioned equally within and between full-sib families. The covariance of relatives within the lines is just as described in Chapter 9, each line being a separate random-breeding population with a total genetic variance of $(1-F)V_G$, on the average. From this we can deduce what the heritability is expected to be within any one line. It will be $(1-F)V_G/[(1-F)V_G + V_E]$, and this reduces to

$$h_t^2 = \frac{h_0^2(1-F_t)}{1-h_0^2F_t} \quad \dots\dots(15.1)$$

where h_t^2 and F_t are the heritability within lines and the inbreeding coefficient at time t , and h_0^2 is the original heritability in the base population. This shows how the heritability is expected to decline with the inbreeding in a small population. The formula, however, is applicable only to characters with no non-additive variance, and in the absence of selection. The operation of natural selection renders the reduction of the heritability less than expected, especially under slow inbreeding. This point has been demonstrated experimentally with *Drosophila* (Tantawy and Reeve, 1956).

Dominance. The components of variance arising from additive genes will have been seen to be independent of the gene frequencies in the base population. When we consider genes with any degree of dominance, however, we find that the changes of variance on inbreeding depend on the initial gene frequencies, and this makes it impossible to give a general solution in terms of the genetic variance present in the base population. We shall therefore do no more than give the conclusions arrived at by A. Robertson (1952) for the case of fully dominant genes, when the recessive allele is at low frequency. This is the situation most likely to apply to variation in fitness arising from deleterious recessive genes, though the effects of selection are here disregarded. Fig. 15.2 shows the redistribution of variance arising from recessive genes at a frequency of $q=0.1$ in the base population. Fig. 15.2(a) refers to full-sib mating with only one family in each line, and Fig. 15.2(b) refers to slow inbreeding. A surprising feature of the conclusions is that the within-line variance at first increases, reaching a maximum when the coefficient of inbreeding is a little under 0.5, and it remains at a fairly high level until

the coefficient of inbreeding approaches 1. The reason, in general terms, for the apparent anomaly that the variation within lines increases during the first stages of inbreeding, can be seen from a consideration of the relationship between the gene frequency and the variance arising from a dominant gene shown in Fig. 8.1(b). The gene frequency is taken to start at a value of 0.1, and on inbreeding it

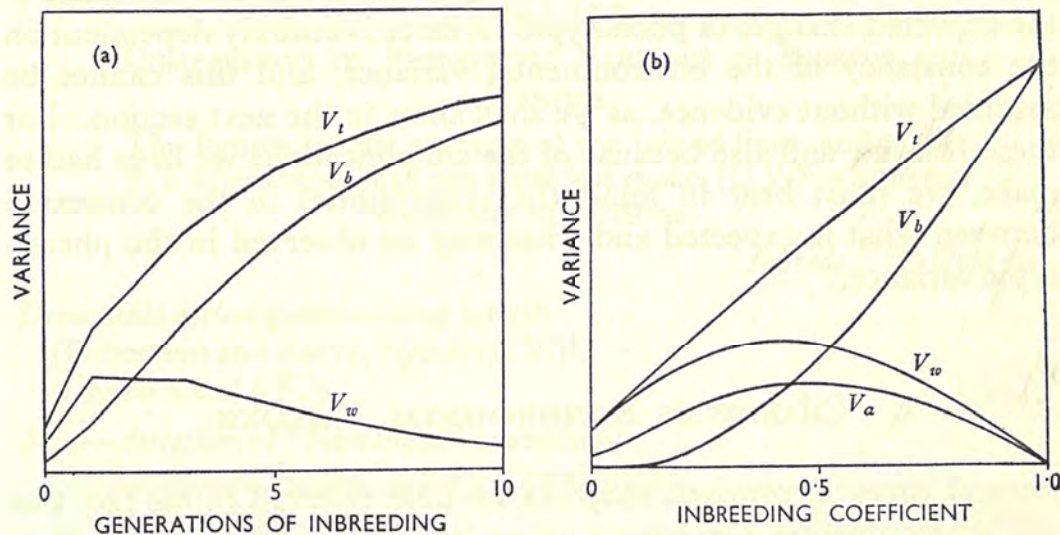


FIG. 15.2. Redistribution of variance arising from a single fully recessive gene with initial frequency $q_0 = 0.1$. (a) with full-sib mating, (b) with slow inbreeding. (From A. Robertson, 1952; reproduced by courtesy of the author and the editor of *Genetics*.)

V_t = total genetic variance.

V_b = between-line component.

V_w = within-line component.

V_a = additive genetic variance within lines.

will increase in some lines and decrease in others, the increase being on the average equal in amount to the decrease. But examination of the graph shows that an increase of gene frequency by a certain amount will increase the variance more than a decrease of the same amount will reduce it. Therefore, on the average, the variance within the lines will increase in the early stages of inbreeding. This increase of variance would be detectable in practice only if a substantial part of the genetic variance were due to recessive genes at low frequencies.

Practical considerations. The extent to which the theoretical changes of variance described in this chapter can be observed in practice depends on how much environmental variance is present. The precise estimation of variance requires a large number of observations and the estimates obtained in practice are usually subject to

rather large deviations due to the chances of sampling. Consequently the changes of variance must usually be quite substantial before they are likely to be readily detected. The genotypic variance, moreover, seldom constitutes the major part of the phenotypic variance. Therefore, in relation to the original phenotypic variance, the expected changes due to inbreeding are usually rather small, and this renders their detection all the more difficult. Furthermore, the detection of the expected changes of phenotypic variance is entirely dependent on the constancy of the environmental variance, and this cannot be assumed without evidence, as we shall show in the next section. For these reasons, and also because of the simplifications we have had to make, we must bear in mind the uncertainties in the connexion between what is expected and what may be observed in the phenotypic variance.

CHANGES OF ENVIRONMENTAL VARIANCE

Several times in previous chapters we have referred to the fact that the environmental component of variance may differ according to the genotype; in particular that inbred individuals often show more environmental variation than non-inbred individuals. This fact has been revealed by many experiments in which the variances of inbreds and of hybrids have been compared. Any difference of phenotypic variance between highly inbred lines and the F_1 between them (i.e. the "hybrid") must be attributed to a difference of the environmental component, because the genetic variance is negligible in amount in the hybrids as well as in the inbred lines. The greater susceptibility of inbreds than of hybrids to environmental sources of variation has been observed in a wide variety of characters and organisms. Some examples are cited in Table 15.2; others will be found in the review by Lerner (1954).

The cause of the greater environmental variance of inbreds is not yet fully understood. It has been suggested that the possession of different alleles at specific loci endows the hybrids with greater "biochemical versatility" (Robertson and Reeve, 1952*b*), which enables them to adjust their development and physiological mechanisms to the circumstances of the environment: in other words that developmental and physiological homeostasis is improved by allelic diversity. On the other hand, it has been suggested (Mather, 1953*a*)

that the reduced homeostatic power of inbreds is to be regarded as a manifestation of inbreeding depression: homeostatic power is likely to be an important aspect of fitness, and would therefore be expected, like other aspects of fitness, to decline on inbreeding. The underlying mechanism, we may presume, would be directional dominance, genes that increase homeostatic power tending on the average to be

TABLE 15.2

COMPARISONS OF PHENOTYPIC VARIANCE IN INBREDS AND HYBRIDS

The figures are the averages of the inbred lines, and of the F_1 's where more than one cross was made. (C.V.)² = Squared coefficient of variation.

	<i>Inbreds</i>	<i>Hybrids</i>
<i>Drosophila melanogaster</i> —wing length (Robertson and Reeve, 1952b) (C.V.) ² . 6 inbreds and 6 F_1 's	2.35	1.24
<i>Mice</i> —duration of "Nembutal" anaesthesia (McLaren and Michie, 1956b). Log minutes. 2 inbreds and 1 F_1	0.0665	0.0165
<i>Mice</i> —age at opening of vagina (Yoon, 1955). Days. 3 inbreds and 2 F_1 's	51.7	17.4
<i>Mice</i> —weight at ages given (Chai, 1957) (C.V.) ² . 2 inbreds and 1 F_1	Birth 3 weeks 60 days 119 98 24	59 47 19
<i>Rats</i> —weight at 90 days (Livesay, 1930.) (C.V.) ² . 3 inbreds and 2 F_1 's	522	170

dominant over their alleles that decrease it. Lerner (1954) sees a causal connexion between variability and fitness. He believes greater stability to be a general property of heterozygotes and regards it as the cause of their greater fitness. Though the increase of environmental variance on inbreeding is a phenomenon of great theoretical interest and some practical importance, too little is known about it to justify a more detailed discussion of its causes here. Comprehensive discussions will be found in Lerner (1954) and Waddington (1957).

There are, however, two further points in connexion with the phenomenon that should be mentioned. The first is a technical matter. If the mean value of the character differs between inbreds

and hybrids, as it frequently does, then it may be difficult to decide on a proper basis for the comparison of the variances. It is necessary to find a measure of the variance that does not merely reflect the difference of mean value, and for this purpose the coefficient of variation is often an appropriate measure. The problem is basically a matter of the choice of scale, and will be discussed again in Chapter 17.

The second point concerns the nature of the environmental variation that is being measured. There is a distinction to be made between the "developmental" variation arising from "accidents of development" on the one hand, and adaptive responses to changed conditions on the other. The developmental variation is a manifestation of incomplete buffering, or canalisation, of development and is generally regarded as being harmful. Inbreds, in so far as they show a greater amount of developmental variation, are therefore less fit than hybrids; they are less well able to adjust their development to different conditions of the environment so as to achieve the optimal phenotype. An adaptive response, in contrast, is a modification of the phenotypic value that is beneficial to the individual, such as for example the thickening of the coat of mammals in response to low temperature. If the greater fitness of hybrids over inbreds extends to adaptive responses we should therefore expect hybrids to show more variation of this sort than inbreds. Thus the nature of the environmental variation has an important bearing on the interpretation of a difference of variability between inbreds and hybrids.

UNIFORMITY OF EXPERIMENTAL ANIMALS

Inbred strains of laboratory animals, particularly of mice, are widely used as experimental material in pharmacological, physiological, and nutritional laboratories, when uniformity of biological material is desired. In some kinds of work, work for example which demands the absence of immunological reactions, it is genetic uniformity that is required, and abundant experience has shown that the inbred strains of mice fully satisfy this requirement. In spite of doubts about how effective natural selection for heterozygotes may be in delaying the progress towards homozygosity, these strains have been proved in practice to be genetically uniform. In the course of their maintenance, however, strains inevitably become split up into

sublines, and it is only within a subline that their genetic uniformity can be relied on. Recent work, described in the two following

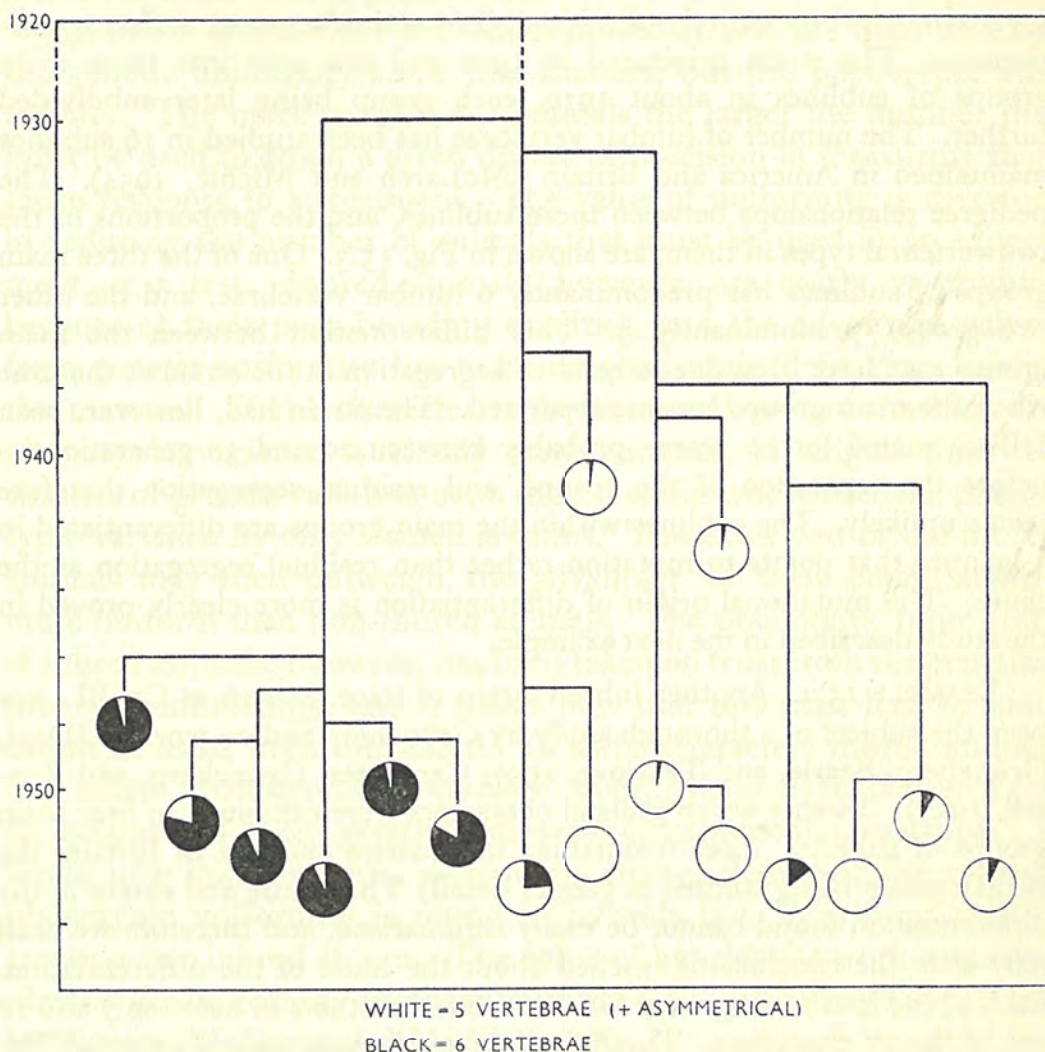


FIG. 15.3. Differentiation between sublines of the C₃H inbred strain of mice, in the number of lumbar vertebrae. Each circle represents a sample of individuals classified for the number of lumbar vertebrae. The proportions of black and white in the circles show the proportions of individuals with 6 and with 5 lumbar vertebrae respectively. (Small proportions of asymmetrical individuals are included with the 5-vertebra classes.) The circles are positioned according to the date of classification, and arranged according to their pedigree relationships. (Data from McLaren and Michie, 1954.)

examples, has revealed genetic differentiation within two widely used strains of mice, and has shown that differences can sometimes be detected between sublines separated by only a few generations.

EXAMPLE 15.1. The inbred strain of mice known as C₃H exhibits variability in the number of lumbar vertebrae, and the sublines differ markedly in this character. Some sublines consist entirely of mice with 5 vertebrae, others entirely of mice with 6, and others with different proportions. The strain originated in 1920 and was split into three main groups of sublines in about 1930, each group being later subdivided further. The number of lumbar vertebrae has been studied in 16 sublines maintained in America and Britain (McLaren and Michie, 1954). The pedigree relationships between these sublines, and the proportions of the two vertebral types in them, are shown in Fig. 15.3. One of the three main groups of sublines has predominantly 6 lumbar vertebrae, and the other two groups predominantly 5. This differentiation between the main groups may have been due to residual segregation in the strain at the time when the main groups became separated. The strain had, however, been full-sib mated for 10 years—probably between 20 and 30 generations—before the separation of the groups, and residual segregation therefore seems unlikely. The sublines within the main groups are differentiated in a manner that points to mutation rather than residual segregation as the cause. The mutational origin of differentiation is more clearly proved in the study described in the next example.

EXAMPLE 15.2. Another inbred strain of mice, known as C₅₇BL, has been the subject of a thorough study by Grüneberg and co-workers (Deol, Grüneberg, Searle, and Truslove, 1957; Carpenter, Grüneberg, and Russell, 1957). Twenty-seven skeletal characters were examined in four main groups of sublines, three maintained in America and one in Britain, the British group being studied in greater detail. The nature and extent of the differentiation found cannot be easily summarised, and therefore we shall only state the conclusions reached about the cause of the differentiation. Each of the four main groups differed from the others in between 7 and 17 out of the 27 characters. The following conclusions were drawn: (1) The differentiation could not reasonably be attributed to residual segregation before the separation of the sublines; and segregation following an accidental outcross was conclusively disproved. (2) Sublines that had been separated for a longer time tended to differ by a greater number of characters than sublines more recently separated. But the magnitude of the difference in any one character was no greater between long-separated sublines than between sublines only recently separated. From this it was concluded that the differences in each character were caused by mutations at single loci. The average difference caused by one mutational step amounted to about 0.6 standard deviation of the character affected.

The study cited in the above example shows that the differences between sublines, though they may be readily detectable, are prob-

ably caused by rather few loci. The differentiation is quite small in comparison with the differences between strains or between individuals in a non-inbred population.

In much of the work for which inbred strains are used it is not the genetic uniformity alone that matters, but the phenotypic uniformity. The more variable the animals the larger the number that must be used to attain a given degree of precision in measuring their mean response to a treatment. The value of uniformity is therefore in reducing the number of animals that must be used in an experiment or a test. Inbred animals, however, are costly to produce because of their poor breeding qualities, and the advantage gained from genetic uniformity has to be weighed against the extra cost of the material. If the character to be measured is one of which the phenotypic variance is chiefly environmental in origin, then the absence of genetic variation in an inbred strain will reduce the phenotypic variance by only a small amount. The extra cost of the inbred animals may then outweigh the advantage of their being slightly more uniform than non-inbred animals. The phenotypic uniformity of inbred animals, however, has been taken on trust from the genetical theory of inbreeding, and it seems now that this trust has, to some extent at least, been misplaced. In some characters inbred animals are more phenotypically variable than hybrid (see Table 15.2) on account of their greatly increased environmental variation. It seems now that for some, perhaps for many, characters the greatest phenotypic uniformity is found in hybrids (i.e. F_1 's) produced by crossing two inbred strains. The value of hybrids for work requiring phenotypic uniformity has been discussed by Grüneberg (1954); and by Biggers, McLaren and Michie (1958).

One final point about the use of inbred and hybrid animals may be noted. An inbred strain or the F_1 of two inbred strains has a unique genotype; and that of an inbred, moreover, is one that cannot occur in a natural population. Testing the response to any treatment on one inbred strain or one hybrid is therefore testing it on one genotype. If there are appreciable differences of response between different genotypes, the experimenter is then not justified in describing his results as referring, for example, to "the mouse."

CHAPTER 16

INBREEDING AND CROSSBREEDING:

III. THE UTILISATION OF HETEROSIS

The crossing of inbred lines plays a major role in the present methods of plant improvement, though in animal improvement it plays a much less important part. In this chapter the genetic principles underlying the use of inbreeding and crossing will be explained, and the various methods described in outline. Technical details, however, will not be given: for these the reader should consult a textbook of plant breeding (e.g. Hayes, Immer, and Smith, 1955). We shall be concerned with outbreeding plants and with animals. But since at first sight the methods applicable to naturally self-fertilising plants are superficially rather like those applicable to outbreeding plants and animals, it will be advisable first to consider very briefly the improvement of self-fertilising plants.

Self-fertilising plants. Each variety of a naturally self-fertilising plant is a highly inbred line, and the only genetic variation within it is that arising from mutation. Genetic improvement can therefore be made only by choosing the best of the existing varieties or by crossing different varieties. The purpose of the crossing is to produce genetic variation on which selection can operate. After a cross has been made, the F_1 and subsequent generations are allowed to self-fertilise naturally. A new population, subdivided into lines, is thus made, and the lines become differentiated as the inbreeding proceeds. Selection is applied by choosing the best lines, which become new and improved varieties. The essential point to note is that what is sought is an improved inbred line, and not a superior crossbred generation: the purpose of the crossing is to provide genetic variation and not to produce heterosis. The process of crossing and selection among the subsequent lines may be repeated cyclically. If two good lines are selected out of the first cross, these may be crossed and a second cycle of selection applied to the derived lines. The genetic properties of a population derived from a cross of two highly inbred lines, such as two varieties of a self-fertilising plant, are peculiar in that all segre-

gating genes have a frequency of 0.5 in the population as a whole. This greatly simplifies the theoretical description of the variances and covariances. Special methods of analysis applicable to such populations have been developed which lead to a separation of the additive, dominance, and epistatic effects, and so provide a guide to the possibilities of improvement in the population of lines derived from a particular cross. For a description of these methods, see Mather (1949), Hayman (1958), and Kempthorne (1957, Ch. 21) where other references are given.

Outbreeding plants, and animals. Applied to naturally outbreeding plants and to animals, the purpose of crossing inbred lines is to produce superior cross-bred, or F_1 , individuals. The utilisation of heterosis in this way depends on selection as well as on the inbreeding and crossing. The selection is applied, in principle, to the crosses, with the aim of finding pairs of lines that cross well, so that the lines may be perpetuated and provide cross-bred individuals for commercial use. In practice, however, the performance of the lines themselves has to be taken into account, because the lines must be reasonably productive if they are to be maintained and used for crossing. This method has been very successful with plants, and has led to an improvement of 50 per cent in the yield of maize grown commercially in the United States, since hybrid seed started to be used in the early 1930's (Mangelsdorf, 1951). Its success with animals, however, has been much less notable. The reasons probably lie chiefly in the greater amount of space and labour required by animals and in their lower reproductive rate, both of which add greatly to the difficulty of producing and testing the inbred lines. During the inbreeding a large proportion of the lines die out from inbreeding depression before a reasonably high degree of inbreeding has been attained. Consequently the inbreeding programme must start with a very large number of lines if enough are to be left after the wastage to give some scope for the selection of good crosses. Another point is that with plants that can be self-fertilised, such as maize, the inbreeding proceeds much faster than with animals. To attain an inbreeding coefficient of, say, 90 per cent would require only 4 years for maize, but 11 years for pigs or chickens, and about 50 years for cattle with a 4- or 5-year generation interval.

Let us now consider the genetic principles on which the utilisation of heterosis depends. It was shown in Chapter 14 that crosses made at random between lines inbred without selection are expected

to have a mean value equal to that of the base population. This is the reason why inbreeding and crossing alone cannot be expected to lead to an improvement, but must be supplemented by selection. In practice some improvement can be expected from the effects of natural selection. It eliminates lethal and severely deleterious genes during the inbreeding, and in so far as these genes affect the desired character an improvement of the cross-bred mean over that of the base population is to be expected. But this improvement will not be very great, because the deleterious genes eliminated will have been at low frequencies in the base population—and the more harmful, the lower the frequency—so that their effect on the population mean will be small. It has been calculated, on the basis of assumptions about the number of loci concerned and their mutation rates, that an improvement of 5 per cent in fitness is the most that could be expected from the elimination of deleterious recessive genes (Crow, 1948, 1952). The bulk of the improvement, therefore, must come from artificial selection applied to the economically desirable characters.

The crossing of inbred lines produces no genotypes that could not occur in the base population. But whereas the best genotypes occur only in certain individuals in the base population, they are replicated in every individual of certain crosses. It is in this replication of a desirable genotype that the chief merit of the method lies. Let us, for simplicity, consider crosses between fully inbred lines. The gametes produced by a highly inbred line are all identical, except for mutation. And the gene content of the gametes of any one line could in principle be found in a gamete from the base population. Therefore the genotype of the F_1 of two lines could in principle be found in an individual of the base population. Thus, provided there has been no selection during the inbreeding, a set of crosses made at random is genetically equivalent to a set of individuals taken at random from the base population; and the individuals of one cross are replicates of one individual in the base population. This replication of a genotype in the individuals of a cross allows the genotypic value to be measured with little error; whereas the genotypic value of an individual in the base population is only crudely measured by its phenotypic value. Further, it is the genotypic value that is measured in the cross and can be reproduced indefinitely, as long as the inbred lines are maintained; whereas only the breeding value can be reproduced by selection of individuals in a non-inbred population. Therefore the condition under which inbreeding and crossing are likely to be a better means of improvement

than selection without inbreeding is when much of the genetic variance of the character is non-additive.

The amount of improvement that can be made by selection among a number of crosses depends on the amount of variation between the crosses. The same relationship holds between the intensity of selection, the standard deviation, and the selection differential as was described in Chapter 11 and illustrated in Fig. 11.3. In the following section the variance between crosses made at random between pairs of lines inbred without selection will be examined.

VARIANCE BETWEEN CROSSES

The variance between crosses to be considered is the variance of the true means of the crosses, or the between-cross component as estimated from an analysis of variance. The variance of the observed means will contain a fraction of the within-cross component for the reasons explained in connexion with family selection in Chapter 13. We shall assume that the experimental design has eliminated all non-genetic sources of variation from the between-cross component.

If the lines crossed are fully inbred there will be no genetic variance within the crosses, and the variance between crosses will be equal to the genotypic variance in the base population, since each cross is equivalent to an individual of the base population. When the lines are only partially inbred, however, some genetic variance will appear within the crosses, and the between-cross variance will be less than with fully inbred lines. It is therefore important to know in what manner the between-cross variance increases as inbreeding proceeds, since this will tell us how much is to be gained by proceeding to high levels of inbreeding.

We noted that crosses between fully inbred lines are genetically equivalent to single individuals of the base population. Crosses between partially inbred lines are analogous, not to individuals, but to families, with degrees of relationship dependent on the inbreeding coefficient of the lines. The variance between families can be formulated in terms of the degree of relationship in the families (Kempthorne, 1954), and this formulation may be extended to crosses by regarding the crosses as families with a relationship depending on the inbreeding coefficient of the lines. The following expression is then obtained for the component of variance between crosses:

T

F, Q, G.

Between-cross variance

$$=FV_A + F^2V_D + F^2V_{AA} + F^3V_{AD} + F^4V_{DD} + \dots \dots\dots (16.1)$$

In this expression V_A and V_D are the additive and dominance variances in the base population; V_{AA} , V_{AD} and V_{DD} are the interaction components as explained in Chapter 8; and F is the inbreeding coefficient of the lines as specified below. The interaction components are included because epistasis may have important effects. Only two-factor interactions, however, are shown: the higher interactions have coefficients in correspondingly higher powers of F . (For every A in the subscript there is a factor F , and for every D a factor F^2 .) The formulation in equation 16.1 is conditional on the following specifications about how the crosses are made. 1. All lines have the same coefficient of inbreeding. 2. All lines have independent ancestry back to the base population; i.e. there is no relationship between the lines. 3. Each cross is made from many individuals of the parent lines; and these individuals are not related to each other within their lines. This means that the genetic variance within the lines is fully represented within the crosses. 4. The coefficient of inbreeding, F , refers not to the individuals used as parents of the crosses, but to their progeny if they were mated within their own lines; in other words, F is the inbreeding coefficient of the next generation of the lines.

Let us now examine the expression 16.1 and consider what it tells us about the variance between crosses. When the inbreeding coefficient is unity the between-cross variance is, as we have already stated, simply the sum of all the components of genetic variance in the base population. During the progress of the inbreeding the contribution of the additive variance increases linearly with F ; those of the dominance variance and of $A \times A$ interactions increases with the square of F ; and the other interaction components with the third or fourth power of F . This means that the dominance and interaction components contribute proportionately more at higher levels of inbreeding than at lower levels. If the character is one with predominantly non-additive variance, the crosses will differ little in merit during the early stages but will differentiate rapidly in the final stages. Since this is the sort of character for which inbreeding and crossing is likely to be the most effective means of improvement, it is clear that inbreeding must be taken to a fairly high level if anything approaching its full benefit is to be realised. Some idea of the level of inbreeding required can be obtained by noting that with $F=0.5$ the between-cross vari-

ance is equal to the variance between full-sib families in the base population. At this level of inbreeding, therefore, the best cross would do no more than replicate the best full-sib family in a non-inbred population.

Combining ability. The components of genetic variance making up the between-cross variance that we have been discussing are causal components, in the sense explained in Chapter 9. The variance between crosses, however, can also be analysed into observational components in the following way. Suppose a set of lines are crossed at random, each line being simultaneously crossed with a number of others. We can then calculate for each line its mean performance, i.e. the mean value of the F_1 's in crosses with other lines. This is known as the *general combining ability* of the line. The performance of a particular cross may deviate from the average general combining ability of the two lines, and this deviation is known as the *special* (or *specific*) *combining ability* of the cross. Or, if we measure the mean values as deviations from the general mean of all crosses, we can express the value of a certain cross as the sum of the general combining abilities of the two lines and the special combining ability of the pair of lines. Thus the mean value of the cross of line X with line Y is

$$M_{XY} = G.C._X + G.C._Y + S.C._{XY} \quad \dots\dots(16.2)$$

where G.C. and S.C. stand for the general and special combining abilities. The variance between crosses can therefore be analysed into two components: variance of general combining abilities and variance of special combining abilities; the latter being, in statistical terms, the interaction component.

The observational components of variance attributable to general and special combining ability are made up of the causal components in the following way.

Variance of crosses attributable to:

$$\left. \begin{array}{l} \text{General combining ability} = FV_A + F^2V_{AA} + \dots \\ \text{Special combining ability} = F^2V_D + F^3V_{AD} + F^4V_{DD} + \dots \end{array} \right\} \dots\dots(16.3)$$

So differences of general combining ability are due to the additive genetic variance in the base population, and to $A \times A$ interactions; and differences of special combining ability are attributable to the non-additive genetic variance. Consequently the variance of general

combining ability increases linearly with F (apart from the interaction component), while the variance of special combining ability increases with higher powers of F . It is therefore the special, and not the general, combining ability that is expected to increase more rapidly as the inbreeding reaches high levels.

EXAMPLE 16.1. An analysis of egg-laying in crosses between highly inbred lines of *Drosophila melanogaster* is reported by Gowen (1952). Five lines were crossed in all ways, including reciprocals, and the numbers of eggs laid by females in the fifth to ninth days of adult life were recorded. The analysis of the crosses yielded the following percentage composition of the variance of egg number:

Variance component	% of total
General combining ability	11.3
Special combining ability	9.7
Differences between reciprocals	2.3
Within crosses	76.6

Thus about half the variance between crosses was due to general, and half to special, combining ability.

Some of the methods of improvement by crossing aim at utilising only the variance of general combining ability, and then the measurement of the general combining ability of the lines becomes an important procedure. In addition to the making of specific crosses between the lines, there are two other methods of measuring general combining ability. A method convenient for use with plants is known as the *polycross* method. A number of plants from all the lines to be tested are grown together and allowed to pollinate naturally, self-pollination being prevented by the natural mechanism for cross-pollination, or by the arrangement of the plants in the plot. The seed from the plants of one line are therefore a mixture of random crosses with other lines, and their performance when grown tests the general combining ability of that line. Another method, applicable also to animals, is known as *top-crossing*. Individuals from the line to be tested are crossed with individuals from the base population. The mean value of the progeny then measures the general combining ability of the line, because the gametes of individuals from the base population are genetically equivalent to the gametes of a random set of inbred lines derived without selection from the base population.

These methods are essentially methods for comparing the general combining abilities of different lines, and so leading to the choice of the lines most likely to yield the best cross, among all the crosses that might be made between the available lines. But if much of the variation between crosses is due to special combining ability, then the general combining ability of two lines will not provide a reliable guide to the performance of their cross.

METHODS OF SELECTION FOR COMBINING ABILITY

The methods of improvement by inbreeding and crossing fall into two groups, according to whether they are designed to utilise only the variation in general combining ability or to utilise also the variation in special combining ability.

Selection for general combining ability. When the improvement of general combining ability only is sought the procedure of selection is much simplified. The general combining abilities of all available lines can be measured, as already explained, without the necessity of making and testing all the possible crosses between them. Some selection can usefully be applied to the lines before they are tested in crosses. There is some degree of correlation between a line's performance as an inbred and its general combining ability, so a proportion of lines can be discarded on the basis of their own performance before the crosses are made. And, finally, there is less to be lost by making the crosses at a relatively low coefficient of inbreeding. Selection for general combining ability may be repeated in cycles, a procedure known in plant breeding as *recurrent selection*. (In animal breeding this term has come to have a different meaning, as will be explained below.) Lines are inbred by self-fertilisation for one or two generations and their general combining abilities tested. The lines with the best general combining abilities are then crossed and a second cycle of inbreeding and selection carried out. A review of the progress made by this method is given by Sprague (1952).

The seed for commercial use is usually not made by a single cross of two lines, but by a *3-way* or *4-way cross*. The object of this is to overcome the generally low production of an inbred used as seed parent. In a 3-way cross the F_1 of two lines is used as seed parent and crossed with a third inbred line. In a 4-way cross two F_1 's of differ-

ent pairs of lines are crossed. The performance of 3-way and 4-way crosses can be reliably predicted from the performance of the constituent single crosses.

Even though selection for general combining ability is widely used in plant breeding and has abundantly proved its success, it is not, perhaps, altogether clear why it is preferred to selection without inbreeding, made either by individual selection or by family selection. Since the variation in general combining ability is attributable to additive variance in the population from which the lines were derived, selection should be effective without inbreeding. Comparisons of the two methods by experiment have not been made on a scale sufficient to prove convincingly the superiority of selection with inbreeding (see Robinson and Comstock, 1955).

Selection for general and specific combining ability. The specific combining ability of a cross cannot be measured without making and testing that particular cross. Therefore to achieve a reasonably high intensity of selection for specific combining ability a large number of crosses must be made and tested. Is no short-cut possible? Could the superior combining ability not be, as it were, built into the lines by selection? From the causes of heterosis explained in Chapter 14 it is clear that what is wanted is two lines that differ widely in the gene frequencies at all loci that affect the character and that show dominance. It should therefore be possible to build up these differences of gene frequency in two lines by selection. Instead of the differences of gene frequency being produced by the random process of inbreeding, they would be produced by the directed process of selection, which would be both more effective and more economical. Two methods based on this idea have been devised. These methods, though originating from plant breeding, provide—in theory at least—the most hopeful means of utilising heterosis in animals. We shall first describe the method known as *reciprocal recurrent selection*, or simply as *reciprocal selection*. In outline, the procedure is as follows.

The start is made from two lines, say A and B. (We shall call them “lines” even though they will not be deliberately inbred.) Crosses are made reciprocally, a number of A ♂♂ being mated to B ♀♀, and a number of B ♂♂ to A ♀♀. The cross-bred progeny are then measured for the character to be improved and the parents are judged from the performance of their progeny. The best parents are selected and the rest discarded, together with all the cross-bred progeny, which

are used only to test the combining ability of the parents. The selected individuals must then be remated, to members of their own line, to produce the next generation of parents to be tested. These are crossed again as before and the cycle repeated. It is seldom practicable to select among the female parents, and the selection is chiefly applied to the males. Each male is mated to several females of the other line so that the judgment of his combining ability may be based on a reasonably large number of progeny. Most of these females are needed to mate to the selected males of their own line for the continuation of the line. Deliberate inbreeding is avoided as far as possible, for the reason to be explained below. The use of all the females as parents in their own lines helps to reduce the rate of inbreeding and allows relatively few males to be used, which intensifies the selection.

An essential prerequisite is that there should be some difference of gene frequency between the two lines at the beginning, or else selection for combining ability will be unable to produce a differentiation of the lines. Any locus at which the gene frequencies are the same in the two lines will be in equilibrium, though an unstable equilibrium. Any shift in one direction or the other will give the selection something to act on and the difference will be increased. The initial difference between the lines may be obtained by starting from two different breeds or varieties, choosing two that already cross well; or by deliberate inbreeding, up to perhaps 25 per cent, and relying on random differentiation of gene frequencies.

Though the performance of the cross is expected to increase under this method of selection, the performance of the lines themselves in respect of the character selected is expected to decrease, for this reason. Characters to which selection would be applied in this way are those subject to inbreeding depression and heterosis; that is to say, those in which dominance is directional. The changes of gene frequency brought about by the selection are toward the extremes, and consequently the mean values of the lines will decline for the reasons explained in connexion with inbreeding in Chapter 14. This decline in the performance of the lines, however, should not be quite as deleterious as the effects of deliberate inbreeding. Inbreeding, as a random process, affects all loci, and the mean values of all characters showing directional dominance decline. But under reciprocal selection it is only the selected character that should decline, except in so far as linked loci are carried along. Nevertheless, reproductive fitness is nearly always a component of economic value, and it is doubtful

how far the distinction will hold. This, however, is the reason why deliberate inbreeding of the lines is to be avoided.

The second method is simpler in procedure than reciprocal selection described above. It was devised as a modification of recurrent selection, intended to utilise special as well as general combining ability (Hull, 1945), and as yet it has no distinctive name. It is known variously as "Hull's modification of recurrent selection," "recurrent selection to inbred tester," "recurrent selection for special combining ability," and in animal breeding simply as "*recurrent selection*." It differs from reciprocal selection in the following way. Instead of starting with two lines and selecting both for combining ability with the other, one starts with only one line and selects it for combining ability with a "tester" line which has previously been inbred. This reduces the amount of effort spent on the testing, and is expected to yield more rapid progress at the beginning because the initial differences of gene frequency between the line and the tester are likely to be more marked. But the ultimate gain is expected to be less than under reciprocal selection, because the general combining ability of the tester line is predetermined, and only the general combining ability of the selected line and the special combining ability of the cross can be improved.

The two methods of selection for special combining ability described in this section are comparatively new methods of improvement and very little practical experience of them has yet been gained. The account of them given here is consequently based almost entirely on theory. Theoretical assessments of their merits in relation to other methods have been made by Comstock, Robinson, and Harvey (1949) and by Dickerson (1952). Though on theoretical grounds they seem promising, the results of the only experiments so far published (Bell, Moore, and Warren, 1955; Rasmuson, 1956) are not encouraging.

Before we leave the subject of inbreeding we must give some further consideration to the particular genetic property that makes selection with inbreeding and crossing preferable to selection without inbreeding. From the theoretical point of view, and leaving all practical considerations aside, the crucial genetic property is overdominance of the genes concerned. The following section is devoted to a consideration of overdominance and its significance.

OVERDOMINANCE

Overdominance is the property shown by two alleles when the heterozygote lies outside the range of the two homozygotes in genotypic value with respect to the character under discussion. Its meaning was illustrated in Fig. 2.3 with respect to fitness as the character, and it has been mentioned from time to time in other chapters. We saw in Chapter 2 how selection favouring heterozygotes leads to a stable gene frequency at an intermediate value, and how this overdominance with respect to fitness probably accounts for much of the stable polymorphism found in natural populations. And in Chapter 12 we saw how overdominance may be a source of non-additive genetic variance in populations that have reached their limit under artificial selection. It is, however, in connexion with the utilisation of heterosis by inbreeding and crossing, or by reciprocal selection, that overdominance has its most important practical consequences. In earlier chapters two basic methods of improvement were distinguished, one being selection without inbreeding, and the other inbreeding followed by crossing. In this chapter we have seen that selection is an integral part of the second method also. The essential distinction therefore lies in the crossing, rather than in the selection. Now, crossing two lines in which different alleles are fixed gives an F_1 in which all individuals are heterozygotes; and this is the only way of producing a group of individuals that are all heterozygotes. In a non-inbred population no more than 50 per cent of the individuals can be heterozygotes for a particular pair of alleles. Consequently, if heterozygotes of a particular pair of alleles are superior in merit to homozygotes, inbreeding and crossing will be a better means of improvement than selection without inbreeding. Furthermore, it is only when there is overdominance with respect to the desired character, or combination of characters, that inbreeding and crossing can achieve what selection without inbreeding cannot. Under any other conditions of dominance the best genotype is one of the homozygotes, and all individuals can be made homozygous by selection, without the disadvantages attendant on inbreeding and much more simply than by methods dependent on crossing. It was stated earlier in this chapter that the potentialities of inbreeding and crossing are greatest when there is much non-additive genetic variance and little additive. Now we see that this is only part of the truth:

in principle inbreeding and crossing can surpass selection without inbreeding only when a substantial part of the non-additive variance is due to overdominance. It is therefore of great practical importance to know whether overdominance with respect to economically desirable characters is a major source of variation. It is also of great theoretical interest to know whether overdominance with respect to natural fitness is a common phenomenon affecting many loci, because natural selection favouring heterozygotes would be a potent factor tending to maintain genetic variation in populations. This point will be discussed further in Chapter 20.

The contribution of overdominance to the variance, and the proportion of loci that show overdominance, are really two different questions. Genes that are overdominant with respect to fitness will be at intermediate frequencies and will therefore contribute much more variation than genes at low frequencies. So overdominance may be a major source of variation and yet be a property of only a few loci.

The evidence concerning overdominance has been comprehensively reviewed by Lerner (1954), who reaches the conclusion that overdominance with respect to fitness and characters closely connected with it is widespread and very important. A contrary view is expressed by Mather (1955*b*) on the grounds that much of what appears to be overdominance with respect to certain characters in plants can be attributed to epistatic interaction. These two conflicting opinions will be enough to show that the problem of overdominance remains still an open question. The aim here is not to discuss the opinions, but to indicate briefly the nature of the evidence.

The evidence concerning overdominance is broadly speaking of two sorts, direct and indirect. The direct evidence comes from the comparison of heterozygotes and homozygotes in identifiable genotypes. The indirect evidence comes from the study of the expected consequences of overdominance as they affect the genetic properties of a population, or the outcome of certain breeding methods. Both sorts of evidence are complicated by linkage. We have to distinguish between overdominance as a property of a single locus, and overdominance as a property of a segment of chromosome, which we shall refer to as apparent overdominance. Unequivocal evidence of overdominance arising from a single locus is scarce because it can only be obtained from a locus that has mutated in a highly inbred line, or from a population in which coupling and repulsion linkages are in

equilibrium. The segregation that can be observed in practice, and that gives rise to the genetic variation in a population, is usually not a segregation of single loci but of segments of chromosome, longer or shorter according to the amount of crossing-over. These segments of chromosome, or units of segregation, can show overdominance even though the separate loci do not. All that is needed to produce some degree of apparent overdominance is two genes, linked in repulsion, and both partially recessive. Its most extreme form is produced by two lethal genes linked in repulsion—a “balanced lethal” system—when the heterozygote of the segment spanned by the two loci is the only viable genotype.

In considering the direct evidence it is necessary to recognise that overdominance may be manifested at different “levels” according to the complexity of the character under discussion. A pair of alleles with pleiotropic effects may be found not to exhibit overdominance when any of the characters they affect is examined separately; yet if natural fitness or economic merit is founded on a combination of these characters, the alleles may show overdominance with respect to fitness or merit. Thus there may be no overdominance at the lower level of the simpler characters, but overdominance at the higher level of the more complex character.

EXAMPLE 16.2. An example of overdominance due to pleiotropy is provided by the pygmy gene in mice, already referred to in several examples in earlier chapters. The gene reduces body size and in the homozygote it causes sterility (King, 1955). In respect of body size it is nearly, but not quite, recessive. In respect of sterility it is probably also nearly recessive, though this was not proved. In neither body size nor sterility separately is there overdominance. But if small size were desirable (as it was in the experiment in which the gene was discovered), then under these conditions the genotype with the highest merit is the heterozygote, since the sterile homozygotes cannot reproduce. With respect to merit, or fitness under these conditions, the gene therefore shows overdominance. The lethal gene in the line of *Drosophila* selected for high bristle number, mentioned in Chapter 12, is another case of the same sort of overdominance; and so also is the sickle-cell anaemia described in Example 2.4.

The observations that provide direct evidence concerning overdominance may be briefly summarised as follows. The experience of Mendelian genetics shows that mutant genes are not commonly overdominant with respect to their main effects. Nor is overdominance with respect to natural fitness at all obvious. Indeed, if there

were more than a mild degree of overdominance with respect to fitness a gene would not be rare enough to be classed as a "mutant." Though the evidence of Mendelian genetics suggests that overdominance is not a very common property of genes, many cases are nevertheless known. Overdominance due to pleiotropy, such as the cases mentioned in the above example, are not infrequent. And, overdominance with respect to certain components of natural fitness has been proved for some of the blood group genes in poultry (see Briles, Allen, and Millen, 1957; Gilmour, 1958).

The nature of the indirect evidence concerning overdominance is, in brief summary, as follows.

1. Experiments on the rate of loss of genetic variance during inbreeding point to the operation of natural selection in favour of heterozygotes (Tantawy and Reeve, 1956; Briles, Allen, and Millen, 1957; Gilmour, 1958). This indicates apparent overdominance, but it does not prove overdominance at the individual loci.

2. Crow (1948, 1952) has given reasons for thinking that the yield of grain obtained from the best crosses between inbred lines of maize is too high to be accounted for without overdominance at some loci. The reasoning depends on assumptions about the number of loci affecting yield and the mutation rates, and the conclusion is therefore tentative. Robinson *et al.* (1956) point out that the reasoning cannot justifiably be applied to maize crosses because the lines crossed generally come from different varieties and not from the same base population as required by Crow's hypothesis.

3. Comstock and Robinson (1952) have devised methods for measuring the average degree of dominance from measurements made on non-inbred populations. Preliminary results from maize (Robinson and Comstock, 1955) suggest that there cannot be overdominance (as distinct from apparent overdominance) at more than a small proportion of the loci that influence the yield of grain.

4. The existence of polymorphism in natural populations, as described in Chapter 2, cannot readily be explained except by supposing that the genes concerned are overdominant with respect to fitness.

From the foregoing outline of the evidence it is clear that the problem of how important overdominance is remains unsolved. Some of the differences of opinion about it may arise from different views of what phenomena are to be included under the term—whether apparent overdominance due to linkage, or overdominance

due to pleiotropy, are to be regarded as overdominance or not. Moreover, the question of how important overdominance is means different things according to whether we are concerned with its frequency as a property of genes, or with the amount of variation it causes.